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The Appropriate Use of Neuroimaging in the Diagnostic Work-Up of Dementia: An Economic Literature Review and Cost-Effectiveness Analysis

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Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. The Evidence Development and Standards branch works with expert advisory panels, clinical experts, scientific collaborators, and field evaluation partners to conduct evidence-based reviews that evaluate the effectiveness and cost-effectiveness of health interventions in Ontario.

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Abstract

Background

Structural brain imaging is often performed to establish the underlying causes of dementia. However, recommendations differ as to who should receive neuroimaging and whether computed tomography (CT) or magnetic resonance imaging (MRI) should be used.

Objectives

This study aimed to determine the cost-effectiveness in Ontario of offering structural imaging to all patients with mild to moderate dementia compared with offering it selectively according to guidelines from the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCC). We compared the cost-effectiveness of CT and MRI as first-line strategies.

Methods

We performed a systematic literature search (2000 to 2013) to identify cost-effectiveness studies of clinical prediction rules and structural imaging modalities. Studies were assessed for quality and applicability to Ontario. We also developed a model to evaluate the cost-effectiveness of clinical guidelines (image all versus according to CCC) and modalities (CT versus MRI). Transition probabilities, utilities, and costs were obtained from published literature or expert opinion. Results were expressed in terms of costs and quality adjusted life years (QALYs).

Results

No relevant cost-effectiveness analyses were identified in the published literature. According to the base-case results of our model, the most effective and cost-effective strategy is to image patients who meet CCC criteria with CT and to follow-up with MRI for suspected cases of space-occupying lesions (SOL). However, the results were sensitive to the specificity of MRI for detecting vascular causes of dementia. At a specificity of 64%, the most cost-effective strategy is CCC followed by MRI.

Limitations

Studies used to estimate diagnostic accuracy were limited by a lack of a gold standard test for establishing the cause of dementia. The model does not include costs to patients and their families, nor does it account for patient preferences about diagnostic information.

Conclusions

Given the relative prevalence of vascular dementia and SOLs, and the improvement in QALYs associated with treatment, the strategy with the greatest combined sensitivity (CCC with CT followed by MRI for patients with SOLs) results in the greatest number of QALYs and is the least costly. Due to limitations in the clinical data and challenges in the interpretation of this evidence, the model should be considered a framework for assessing uncertainty in the evidence base rather than providing definitive answers to the research questions.

Plain Language Summary

There is wide debate about whether or not brain scans should routinely be used to assess patients with mild to moderate dementia. Proponents say that imaging is important to detect or rule out possible underlying causes of dementia, such as silent strokes and tumours. Opponents call for a more selective approach, considering the need for clinical judgement and the cost of the technology. Using data from published research, a model was developed to study the cost-effectiveness of different approaches to brain imaging for a hypothetical group of patients with dementia. The model compared 2 strategies: imaging all patients and imaging selectively based on clinical practice guidelines from the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCC). It also compared 2 types of technology: computed tomography (CT) and magnetic resonance imaging (MRI).

The results of the model depended on the accuracy of CT and MRI in diagnosing dementia caused by vascular disease. Unfortunately, because there is no "gold standard" approach to diagnosing dementia, interpreting the published research is challenging. Based on current evidence, in which diagnostic strategies are assessed using a mix of methods, the model showed that the most effective and least costly strategy is to image selectively according to the CCC guidelines, using CT first and then MRI as a follow-up for patients suspected of having space-occupying lesions such as tumours. However, if we assumed that MRI plus clinical assessment is the gold standard, then imaging all patients with MRI is the most cost-effective strategy, despite the higher cost of this technology.

The model did not take into account the value that physicians, patients, and families place on having diagnostic information, even if effective treatment does not yet exist. The model was not able to answer the specific research questions with confidence, but it provides a framework for identifying areas where more research is needed to support decision-making in the diagnosis of dementia.

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List of Abbreviations

AAN	American Academy of Neurology
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer disease
BT	Brain tumour
CCC	Canadian Consensus Conference on the Diagnosis and Treatment of Dementia
CT	Computed tomography
DSC MRI	Dynamic susceptibility contrast magnetic resonance imaging
DSM	Diagnostic and Statistical Manual of Mental Disorders
EBA	Evidence-based analysis
FDG	Fluorodeoxyglucose 18F
FN	False negative
FP	False positive
HQO	Health Quality Ontario
HUI	Health Utilities Index
ICD	International Classification of Disease
ICER	Incremental cost-effectiveness ratio
LR	Likelihood ratio
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association
NPH	Normal-pressure hydrocephalus
OHTAC	Ontario Health Technology Advisory Committee
PET	Positron emission tomography
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial
SDH	Subdural hematoma
SOL	Space-occupying lesion
SPECT	Single-photon emission computed tomography
THETA	Toronto Health Economics and Technology Assessment
TN	True negative
TP	True positive
VaD	Vascular dementia

Background

The Toronto Health Economic and Technology Assessment (THETA) Collaborative was commissioned by Health Quality Ontario (HQO) to evaluate the appropriate use of neuroimaging in the assessment of patients with suspected dementia. This report summarizes the methods and results of the systematic economic literature review and original economic evaluation developed for this analysis.

Health Quality Ontario conducts full evidence-based analyses, including economic analyses, of health technologies being considered for use in Ontario. These analyses are then presented to the Ontario Health Technology Advisory Committee, whose mandate it is to examine proposed health technologies in the context of available evidence and existing clinical practice, and to provide advice and recommendations to Ontario health care practitioners, the broader health care system, and the Ontario Ministry of Health and Long-Term Care.

DISCLAIMER: Health Quality Ontario uses a standardized costing method for its economic analyses. The main cost categories and associated methods of retrieval from the province's perspective are described below.

Hospital costs: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency department visit, and day procedure costs for the designated International Classification of Diseases diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in the estimated costs of the diagnoses and procedures under consideration. Due to difficulties in estimating indirect costs in hospitals associated with a particular diagnosis or procedure, Health Quality Ontario normally defaults to a consideration of direct treatment costs only.

Non-hospital costs: These include physician services costs obtained from the Ontario Schedule of Physician Benefits, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible, or from the device manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied (to both costs and effects/QALYs), as recommended by economic guidelines.

Downstream costs: All reported downstream costs are based on assumptions of population trends (i.e., incidence, prevalence, and mortality rates), time horizon, resource utilization, patient compliance, health care patterns, market trends (i.e., rates of intervention uptake or trends in current programs in place in the province), and estimates of funding and prices. These may or may not be realized by the Ontario health care system or individual institutions and are often based on evidence from the medical literature, standard listing references, and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach.

The economic analysis represents ***an estimate only***, based on the assumptions and costing methods explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

NOTE: Numbers may be rounded to the nearest decimal point, as they may be reported from an Excel spreadsheet

Overuse, underuse, and misuse of interventions are important concerns in health care and lead to individuals receiving unnecessary or inappropriate care. In April 2012, under the guidance of the Ontario Health Technology Advisory Committee's Appropriateness Working Group, Health Quality Ontario (HQO) launched its Appropriateness Initiative. The objective of this initiative is to develop a systematic framework for the ongoing identification, prioritization, and assessment of health interventions in Ontario for which there is possible misuse, overuse, or underuse.

For more information on HQO's Appropriateness Initiative, visit our website at www.hqontario.ca.

Dementia is a term used to describe symptoms that may include persistent impairment of memory, language, and visual-spatial ability, in addition to other cognitive and personality disorders. The most frequently used criteria for the diagnosis of dementia are described by the Diagnostic and Statistical

Manual (DSM), International Classification of Disease (ICD), or National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA). The severity of dementia is defined using cognitive tests, such as the Mini-Mental State Examination (MMSE).

Dementia can be caused by a number of different pathological processes that can be difficult to distinguish by clinical evaluation alone. Further investigation, including structural imaging of the brain, is often undertaken to establish the cause of illness for patients who meet criteria for dementia according to the DSM, ICD, or NINCDS-ADRDA. Several committees have published recommendations for the diagnostic evaluation of people with dementia. (1-7) In Ontario, the most frequently used guidelines include those developed by the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCC) (4) and the American Academy of Neurology (AAN). (5) Both recommend a complete neurologic history, neuropsychological assessment, and laboratory work-up as essential components of the diagnostic pathway. However, they differ with respect to who should receive neuroimaging and whether this should be performed using computed tomography (CT) or magnetic resonance imaging (MRI) (Table 1).

Table 1: Guidelines for Assessment of Dementia

Guideline, Year	Indications for Structural Imaging	Recommendation
CCC, 2012 (4)	Age < 60 years Rapid (e.g., 1 or 2 months) unexplained decline in cognition or function "Short" duration of dementia (< 2 years) Recent and significant head trauma Unexplained neurological symptoms (e.g., new onset of severe headache or seizures) History of cancer (especially in sites and types that metastasize to the brain) Use of anticoagulants or history of bleeding disorder History of urinary incontinence and gait disorder early in the course of dementia (as may be found in normal-pressure hydrocephalus) Any new localizing sign (e.g., hemiparesis or a Babinski reflex) Unusual or atypical cognitive symptoms or presentation (e.g., progressive aphasia) Gait disturbance	Structural imaging is not required in all people with dementia, although it is indicated in most. Although more costly and less available, MRI is preferable to CT.
AAN, 1994 (1)	Insidious onset of dementia before age 60 years Focal signs or symptoms Seizures Gait disturbance	The official position of the AAN is that neuroimaging need not be obtained routinely, as defined in the official AAN practice parameter. However, the published background paper for the AAN guideline recommends that every patient with dementia undergo a neuroimaging procedure at least once. The expert panel indicated that to their knowledge everyone in the US is imaged unless contraindicated.
AAN, 2001 (5)	No criteria given	

Abbreviations: AAN, American Academy of Neurology; CCC, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia; CT, computed tomography; MRI, magnetic resonance imaging; US, United States.

The primary objectives of structural neuroimaging are to exclude potentially treatable causes of dementia, such as a tumour, and to assess specific causes of dementia, neurodegenerative or otherwise. A perfect diagnostic strategy would enable the physician to identify all patients with space occupying lesions (SOL) and cerebrovascular causes of dementia. But no diagnostic strategy is perfect; a trade-off must be made to avoid overtesting while capturing as many cases of treatable disease as possible. When neuroimaging is deemed appropriate, the physician must also decide whether to offer CT or MRI in the first instance. CT is more widely available and is useful for excluding medium to large intracranial lesions. However, MRI is the modality of choice for assessing many specific causes of dementia.

The desirability of a particular diagnostic strategy depends not only on its sensitivity and specificity and on disease prevalence, but also on the relative value of each diagnostic outcome in terms of morbidity, morality, and health-related quality of life. (8) In theory, the most robust evidence of diagnostic utility of a medical test comes from a properly designed randomized trial. In practice, these trials are rarely feasible due to the large number of competing strategies and indirectness of the link between test performance and patient outcomes. (8) For most diagnostic tests, this link must be deduced from evidence reported across different studies, and decisions must be made irrespective of the availability of evidence. Studies of test performance must be used to inform the ability of tests to discriminate between disease and nondisease; the prevalence of disease conditions is reported in epidemiological studies; and treatment effect is studied in clinical trials.

It is in these cases that decision modelling is most useful. Decision models provide a transparent, reproducible approach to synthesizing many different types of evidence in order to evaluate the trade-off between the benefits, risks, and costs of multiple alternative strategies. Models can be particularly useful for exploring the diagnosis of diseases with few effective treatments, such as dementia. (8) Models allow us to describe the conditions under which it would be worthwhile to employ particular tests. They can also provide a conceptual framework to identify what types of comparative evidence are needed to evaluate tests. (9)

Expert Panel

In April 2013, an Expert Advisory Panel for Appropriate Utilization of Medical Imaging for the Diagnostic Work-Up in Patients with Dementia was struck. Members of the panel included family physicians, neurologists, neuro/radiologists, geriatricians and geriatric psychiatrists, personnel from the Ministry of Health and Long-Term Care, and physicians recruited through the Ontario Medical Association.

The role of the expert panel was to contextualize the evidence produced by Health Quality Ontario and provide advice on the appropriate use of diagnostic imaging in dementia diagnosis. However, the statements, conclusions and views expressed in this report do not necessarily represent the views of panel members.

Objectives

This study had 2 objectives. First, we aimed to determine which clinical indications for structural imaging are most cost-effective for the diagnosis of suspected dementia. Second, we sought to determine which modality is most cost-effective when structural imaging is indicated.

Economic Analysis

Research Questions

- Which clinical guideline for structural imaging is most effective and cost-effective for the diagnosis of people with mild to moderate dementia?
- Where structural imaging is indicated, which modality—CT or MRI—is most effective and cost-effective?

Economic Literature Review

Methods

We searched Ovid MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, Wiley Cochrane, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), Centre for Reviews and Dissemination/International Agency for Health Technology Assessment, and EconLit from January 1, 2000, to February 22, 2013, to identify studies comparing different clinical prediction rules using CT and MRI. The full literature search strategy is described in Appendix 1.

Potentially relevant studies were identified based on the title and abstract sifting. Full-text articles were retrieved and evaluated.

Inclusion Criteria

- Cost-utility analyses (studies that report outcomes in terms of costs and quality-adjusted life-years [QALYs]) were prioritized for inclusion.
- Where these studies were not available for a particular intervention, we considered cost-effectiveness, cost-benefit, and cost-consequence analyses. In the absence of these types of analysis, we also considered costing studies.
- Studies that evaluated different risk prediction algorithms using structural imaging modalities in people with mild to moderate dementia were included.

Exclusion Criteria

- Abstracts, posters, reviews, letters/editorials, foreign language publications, and unpublished studies
- Studies using functional imaging or conducted in patients with mild cognitive impairment

Results of Economic Literature Review

From a total of 1,563 abstracts, 32 full-text articles were retrieved and 5 were identified as potentially relevant. Two studies (10;11) were excluded as they compared a conventional diagnostic algorithm with one including positron emission tomography (PET), which is not approved for the diagnosis of dementia in Ontario. Two additional studies (12;13) were identified by bibliographic searching but were excluded because they fell outside our prespecified search dates.

Two cost-utility models (14;15) and 1 utility model (16) of the diagnosis of dementia with CT and dynamic susceptibility contrast (DSC) MRI were included. The primary objective of all 3 studies was to evaluate the benefit of functional neuroimaging in addition to examination with standard diagnostic strategies in the setting of a specialized Alzheimer disease centre. Although our protocol does not include functional imaging, we included these studies as some comparators were relevant to our research questions. A summary of each included study is presented in Table 2. Please refer to Appendix 2 for a detailed description of each study.

All 3 studies used a decision analytic model—nearly identical to that first described by Neumann et al (17)—of the diagnosis, drug treatment, and care costs for patients with dementia. In all studies, the baseline "current standard" therapy was defined as the clinical evaluation recommended by the American Academy of Neurology (AAN), which included a complete history, physical, neuropsychiatric evaluation, and CT structural imaging. McMahon et al (14) compared the cost-effectiveness of single-photon emission computed tomography (SPECT) or DSC MRI to standard diagnostic work-up with CT. In a later study, the authors included PET and compared no diagnosis versus a treat-all strategy. Visual SPECT was excluded as it was dominated by all strategies in their previous analysis.

Kulasingam et al (16) evaluated the effectiveness of the AAN guidelines with CT, compared with PET and a no-imaging/treat-all strategy. Although not a cost-utility study (QALYs were reported as the primary outcome but costs were not included), we included this study in our review as it was the only article to evaluate the effectiveness of alternative strategies in different populations, including people at high risk of dementia due to family history, mild cognitive impairment, and mild dementia.

Compared to CT, a treat-all strategy was found to result in an incremental cost of $141,176 per QALY gained, (15) while DSC MRI had an incremental cost-effectiveness ratio of $479,500 per QALY gained. (14) SPECT (visual and computed) was found to be less effective and more expensive than all other strategies in both studies. (14;15) The authors of these studies concluded that standard diagnostic work-up with CT was the most cost-effective strategy for the diagnosis of people with mild to moderate dementia.

The models were sensitive to changes in drug effectiveness and adverse events. Sensitivity analyses showed that relative to CT, the cost-effectiveness of MRI improved with increasing drug effectiveness. The treat-all strategy was dominated by MRI when either the incidence or disutility of drug-associated side effects was increased. (15)

The authors did not address the small difference in QALYs between the 2 studies by McMahon (Table 2). The variation could be due to the different versions of the Health Utilities Index (HUI) used: HUI Version 2 in the first study (14) and HUI Version 3 in the second. (15) It may also be explained by small changes in the natural history transition probabilities used in the model.

A major limitation of both cost-utility studies was that they included DSC MRI, which is a non-standard MRI requiring gadolinium (contrast-injection) to examine tissue perfusion. The expert panel indicated that it may only be possible to order such scans in Ontario for research purposes. Both studies were conducted from a United States societal perspective, in which patient time and transportation costs are taken into account; this makes it challenging to apply the findings to Ontario. However, in sensitivity analyses, both studies excluded patient costs and found no change in their conclusions. They were also limited by an 18-month time horizon, which will underestimate the benefit of reducing mortality by slowing disease progression.

Table 2: Summary of Studies Included in Economic Literature Review

Perspective, Time Horizon	Population	Comparators	Total Costs	Total QALYs	Incremental Cost per QALY Gained	Uncertainty
McMahon et al, 2000 (14)						
USA; societal 18 months	Mild to moderate dementia[a]	1) AAN with CT 2) AAN with DCS MRI 3) AAN with V SPECT 4) AAN with C SPECT	**CT:** $54,762 **DCS MRI:** $55,769 **V SPECT:** $55,362 **C SPECT:** $55,549	**CT:** 0.989 **DCS MRI:** 0.991 **V SPECT:** 0.985 **C SPECT:** 0.989	V SPECT and C SPECT were dominated by MRI, which had an ICER of $479,500 per QALY compared to CT.	Treat-all strategy dominated all other options in SA but was excluded on the basis that the goal of the model was to evaluate functional imaging.
McMahon et al, 2003 (15)						
USA; societal 18 months	Mild to moderate dementia[a]	1) AAN with CT 2) AAN with DSC MRI 3) AAN with PET 4) AAN with C SPECT 5) Treat all	**CT:** $56,859 **DCS MRI:** $57,877 **PET:** $58,590 **C SPECT:** $58,872 **Treat all:** $57,339	**CT:** 0.709 **DCS MRI:** 0.711 **PET:** 0.706 **C SPECT:** 0.709 **Treat all:** 0.713	PET and C SPECT were dominated by treat all and MRI, which had ICERs of $141,200 and $598,800 per QALY gained, respectively.	Results were sensitive to the effectiveness of treatment for AD; as effectiveness increased, DSC MRI became increasingly cost-effective
Kulasingam et al, 2003 (16)						
USA; costs not reported Lifetime	High risk of AD[b] MCI Mild dementia	1) AAN with CT 2) AAN with PET 3) No test/no treat	Not evaluated	**High risk of AD** CT: 12.25 PET: 12.13 No test: 12.11 **MCI** CT: 6.66 PET: 6.65 No test: 6.58 **Mild dementia** CT: 4.10 PET: 4.09 No test: 4.02	The AAN strategy resulted in the greatest QALY gain across all populations. Costs not included in this analysis.	

Abbreviations: AAN, American Academy of Neurology; AD, Alzheimer disease; C SPECT, single-photon emission computed tomography; CT, computed tomography; DSC MRI, dynamic susceptibility contrast magnetic resonance imaging; ICER: incremental cost-effectiveness ratio; MCI, mild cognitive impairment; PET, positron emission tomography; QALY, quality-adjusted life-year; V SPECT, visual single-photon emission computed tomography.

[a]Patients presenting to a specialized Alzheimer disease centre.

[b]At elevated risk of Alzheimer disease due to family history.

Original Cost-Effectiveness Analysis

No recently published studies have evaluated the cost-effectiveness of different guidelines for neuroimaging or different structural imaging modalities for the diagnosis of people with dementia. At the request of the expert panel, we developed an original cost-utility analysis from the perspective of the Ministry of Health and Long-Term Care, with the aim of determining which clinical prediction rule for structural imaging is most cost-effective and whether CT or MRI is the more cost-effective modality.

Consistent with economic literature in this area, the model was built using a cycle length of 6 weeks. A standard annual discount rate of 5% was applied to both costs and QALYs. The model was run over the lifetime of the hypothetical cohort (i.e., until everyone in the cohort had died).

Methods

A probabilistic cost-utility analysis using a Markov model was developed using the decision analysis software TreeAge Pro 2012. Estimates of diagnostic utility and prevalence were obtained from the clinical evidence-based analysis (EBA) conducted by Health Quality Ontario. (18) Estimates used to inform natural history, treatment effectiveness, costs, and utilities were obtained from published literature and expert opinion. Results were reported in terms of costs (2012 Canadian dollars), QALYs, and incremental cost per QALY gained.

Population

The hypothetical population evaluated by the model included people with mild to moderate dementia as diagnosed by standard criteria (NINCDS-AIREN, DSM-III-R, or DSM-IV). Based on studies used to inform estimates of diagnostic accuracy and disease progression, this hypothetical cohort had an average age of 70 years and 65% were female.

The aim of this analysis was to evaluate the most effective and cost-effective clinical indications for imaging and imaging modality from the perspective of the primary care practitioner. Therefore, estimates used to inform the prevalence of different forms of dementia in the base-case analysis were derived from studies conducted in community population.

Based on the ratio of mild to moderate cases in the economic literature and confirmed by expert opinion, it was assumed that approximately 60% of people presenting to primary care with dementia symptoms have a mild form of the condition. The model did not consider people with severe dementia; it was assumed that these people would have sought medical attention at an earlier stage in the disease course. All were assumed to be living in the community, not in nursing homes, at the time of presentation to their primary care provider. As per protocol, the model did not consider people with mild cognitive impairment or those with undiagnosed dementia.

Comparators

Consistent with studies included in the EBA, clinical indications for imaging were defined based on validated prediction rules. For the purpose of the model, the expert panel indicated that the rules most clinically relevant to current practice in Ontario are those developed by the CCC and the AAN.

These guidelines have the common objective of helping physicians decide when to request a brain scan to investigate dementia that might be caused by a condition amenable to treatment. In the case of lesions such as a subdural hematoma (SDH), normal-pressure hydrocephalus (NPH), or brain tumour (BT), the best outcome would be the reversal of cognitive impairment. For patients with vascular disease, good outcomes may include a more informed approach to cardiovascular risk management.

Two studies (19;20) were identified that evaluated the diagnostic accuracy of the CCC and AAN guidelines, but only with respect to detecting space-occupying lesions (SOL). A study by Sitoh et al (21) has been the only one to evaluate a guideline's utility in detecting vascular dementia; however, this study did not include the AAN guidelines. Because by definition the population who do and do not undergo imaging will differ between guidelines, we cannot assume that the diagnostic accuracy observed for the CCC guidelines can be used as a proxy for AAN. Therefore, it was not possible to establish a meaningful comparison of these guidelines, and the AAN prediction rules were not included in the analysis. Instead, an image-all strategy was included to provide an additional clinically plausible alternative; the expert panel advised that a no-imaging/treat-all strategy would be below an acceptable standard of care.

In Ontario, first-line imaging options include CT and MRI. Functional imaging, such as PET and SPECT, were excluded as they are not currently licenced for the diagnosis of dementia in Canada. Each prediction rule and imaging modality was evaluated in sequence, resulting in a total of 4 alternative strategies. Details of the strategies are provided in Table 3.

Table 3: Comparators Included in Base-Case Economic Evaluation

Strategy	Appropriateness for Imaging	Structural Imaging Modality
1) Image all with CT followed by MRI for SOL	All patients were clinically assessed. All received neuroimaging.	Patients were evaluated using CT in the first instance. Those who tested positive for SOL received MRI.
2) Image all with MRI only	All patients were clinically assessed. All received neuroimaging.	Patients were evaluated using MRI in the first instance.
3) CCC with CT followed by MRI for SOL	All patients were clinically assessed. Appropriateness for structural imaging was based on CCC clinical prediction rules.	Patients were evaluated using CT in the first instance. Those who tested positive for SOL received MRI.
4) CCC with MRI only	All patients were clinically assessed. Appropriateness for structural imaging was based on CCC clinical prediction rules.	Patients were evaluated using MRI in the first instance.

Abbreviations: CCC, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia; CT, computed tomography; MRI, magnetic resonance image.; SOL, space-occupying lesion.

Approach to Modelling

Patients entered the model after receiving a diagnosis of mild to moderate dementia following a standard clinical assessment. This assessment typically includes patient history; physical, mental status, and neurological examinations; and blood and urine tests. It was assumed that patients with cognitive complaints or dementia caused by medication, alcohol, metabolic disorders, infection, depression, and recent physical trauma would be identified at this initial stage.

To comprehensively quantify the costs and consequences associated with each true positive (TP), false positive (FP), true negative (TN), and false negative (FN), information on the natural history and differential response to treatment for each potential cause of dementia was required. Space-occupying lesions and neurodegenerative causes of dementia were each represented according to the 3 most prevalent illnesses in each category, according to Clarfield (22): NPH, SDH, and BT (for SOLs) and vascular dementia (VaD), Alzheimer disease (AD), and AD with cerebrovascular disease (for neurodegenerative causes). The most common other causes of neurodegenerative dementia (Lewy body dementia, Parkinson disease dementia) progress similarly to AD and are treated similarly. Dementia due

to rarer conditions such as frontotemporal dementia, Huntington disease, and Creutzfeldt-Jacob disease were not included due to time limitations; these conditions occur in smaller numbers and were not expected to impact the overall outcomes of the model. Data used to inform disease prevalence and diagnostic utility are reported in Table 4. Data used to inform natural history, treatment effectiveness, and costs are described in detail in the Model Parameters section below.

The general approach to modelling each strategy is illustrated in Figures 1 to 4. Each decision tree has one decision node that illustrates 4 options: image all with MRI; image all with CT followed by MRI; image according to CCC guidelines with MRI; image according to CCC guidelines with CT followed by MRI.

The CCC options yield 2 chance events: the patient is eligible for imaging according to the guidelines, or is not. Eligible patients undergo either CT or MRI as dictated by the strategy under consideration. Those in the treat-all strategies all receive either CT or MRI.

Note that all diagrams are schematic. In the model, multiple transitions were restructured into a number of conditional probabilities so that each set of transitions is a series of binary events. This ensures that probabilities less than 0 or greater than 1 cannot occur during simulation.

The probability that a patient tested positive for SOL was calculated based on the pretest probability of disease and the sensitivity and specificity of the imaging modality. Because the CCC is itself a diagnostic test, the post-test probability of SOL and VaD was calculated using the sensitivity and specificity of the guideline and was used to inform the pretest probability for CT and MRI. The baseline prevalence of SOL was equal to the pretest probability for patients in the image-all strategy.

The probability that a patient has an SOL given a positive result is commonly referred to as the positive predictive value of the test. The probability that the patient does not have an SOL given a negative disease finding is referred to as the negative predictive value. These probabilities were also derived from the pretest probability of the disease and the sensitivity and specificity of the imaging modality. All patients in this pathway were assessed and/or treated, incurring the costs and benefits described below for each natural history model. The probability of a patient within this group having NPH, SDH, or BT was based on the relative reported prevalence of each of these conditions.

All patients correctly diagnosed with AD and mixed dementia were treated with acetylcholinesterase inhibitors (AChEIs). If patients were diagnosed using CT, the prevalence of antiplatelet agent use remained as reported in the general population. If they were diagnosed using MRI, antiplatelet agent use was halved among patients with evidence of hemorrhagic stroke and doubled in those with ischemic stroke. The risk of secondary stroke was calculated accordingly.

It was assumed that all those who did not receive imaging were treated with AChEIs. As a result, all patients correctly assessed as having AD (rather than vascular dementia or SOLs) incurred the costs and benefits associated with treatment. Patients with mixed vascular disease also benefited from treatment. None received cardiovascular risk modification. Those with SOL incurred the cost of AChEI treatment and did not receive treatment for their condition.

Key Assumptions

The model was developed around estimates of diagnostic accuracy reported in a primary study by Sitoh et al (21) and a meta-analysis by Beynon et al. (23) These studies, and indeed all studies in this disease area, are limited by lack of a consistent reference standard. While Sitoh and colleagues (21) used CT as the gold standard to evaluate the presence of SOL and vascular dementia, the studies included in Beynon et al (23) evaluated the accuracy of MRI and CT scans against many different clinical criteria.

The absence of a gold standard presented 2 key limitations. First, although we would expect that MRI with clinical assessment would represent the gold standard in imaging for vascular dementia, the majority of studies seem to have assessed the presence or absence of disease based on radiographic information alone. Therefore, although more sensitive than CT, MRI was reported to be much less specific. Second, because studies have shown that CT and MRI perform differently in the detection of SOL and vascular disease, we would expect that, had Sitoh et al used MRI as their reference standard, the CCC would be associated with different estimates of sensitivity and specificity.

To address these issues, our base-case analysis assumed that the results reported by Sitoh et al represent a "true" estimate of accuracy of the CCC guideline. The reported specificity of MRI was used as the base-case value. The reported diagnostic accuracy of CT and MRI was then applied to those assessed as eligible for imaging according to reported CCC criteria.

The expert panel indicated that the primary advantage of MRI compared with CT is its ability to detect underlying strokes and microbleeds. This allows physicians to appropriately manage cardiovascular risk factors. It was assumed that, within the model population, 36% of patients were taking antiplatelet agents for general cardiovascular protection. When patients received CT imaging, the prevalence of antiplatelet agent use in the group was unchanged. However, when patients received MRI, this proportion was halved among those with evidence of hemorrhagic stroke and doubled in people with ischemic lesions, in accordance with published estimates. For patients without cerebrovascular disease (i.e., with NPH, SDH, BT, or AD), antiplatelet agents were assumed to neither benefit nor harm.

Uncertainty

The model was built probabilistically to take account of the uncertainty surrounding each parameter. To characterize this uncertainty, a probability distribution was defined for each value based on reported standard error, confidence interval, or sample size in the data sources. The way in which distributions were defined reflected the nature of the data (e.g., beta distributions were used for probabilities; gamma distributions for costs; and lognormal distributions for estimates of relative effect). (24) When the model was run, a value for each parameter was randomly selected from its respective distribution. The model was run repeatedly (15,000 times) to obtain mean cost and QALY values.

Sensitivity analyses were also undertaken to test the robustness of the model to changes in assumptions and data sources. In these analyses, one or more parameters were changed and the analysis was rerun to evaluate the impact of these changes on the results of the model.

Validation

The structure and data used to inform the model were approved by the expert panel as a reasonable simplification of the decision making and disease processes. The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given the inputs. The model was peer-reviewed by a second experienced health economist from THETA; this included systematically checking the model calculations.

Interpretation

The results of cost-effectiveness analyses are presented as incremental cost-effectiveness ratios (ICERs). ICERs are calculated by dividing the difference in costs associated with 2 alternative strategies by the difference in QALYs.

Where more than 2 strategies are compared, the ICER is calculated according to the following process:

- The interventions are ranked in terms of cost, from least to most expensive.
- If an intervention is more expensive and less effective than the preceding intervention, it is said to be "dominated" and is excluded from further analysis.
- ICERs are then calculated for each strategy compared with the next most expensive non-dominated option. If the ICER for an intervention is higher than that of the next most effective strategy, then it is ruled out by "extended dominance."
- ICERs are recalculated, excluding any strategies subject to dominance or extended dominance.

When there are multiple comparators, the option with the greatest average net benefit may also be used to rank comparators. An intervention is said to be cost-effective if it is less expensive and more effective than alternative options, or if the increased cost of an intervention is deemed to be justified by its increased effectiveness (i.e., it offers "value for money").

Sensitivity Analyses

Several types of sensitivity analysis (probabilistic, 1- and 2-way, threshold, and structural) were conducted to explore key sources of variability and uncertainty within the model. One-way sensitivity analysis refers to the process of varying one parameter in a range between an upper and lower bound while all other parameters are kept constant. A series of one-way sensitivity analyses is the easiest way to identify which parameters have the greatest effect on the optimal decision. The point at which the decision shifts from one alternative to another is often referred to as the crossover point or threshold. In some cases it may not be clinically plausible to explore uncertainty in one parameter at a time. For example, altering sensitivity without specificity is not usually possible. In this case, 2-way sensitivity analysis is performed, preferably choosing paired values of sensitivity and specificity along a receiver operating curve. The methods and results of sensitivity analyses are presented in the Results section.

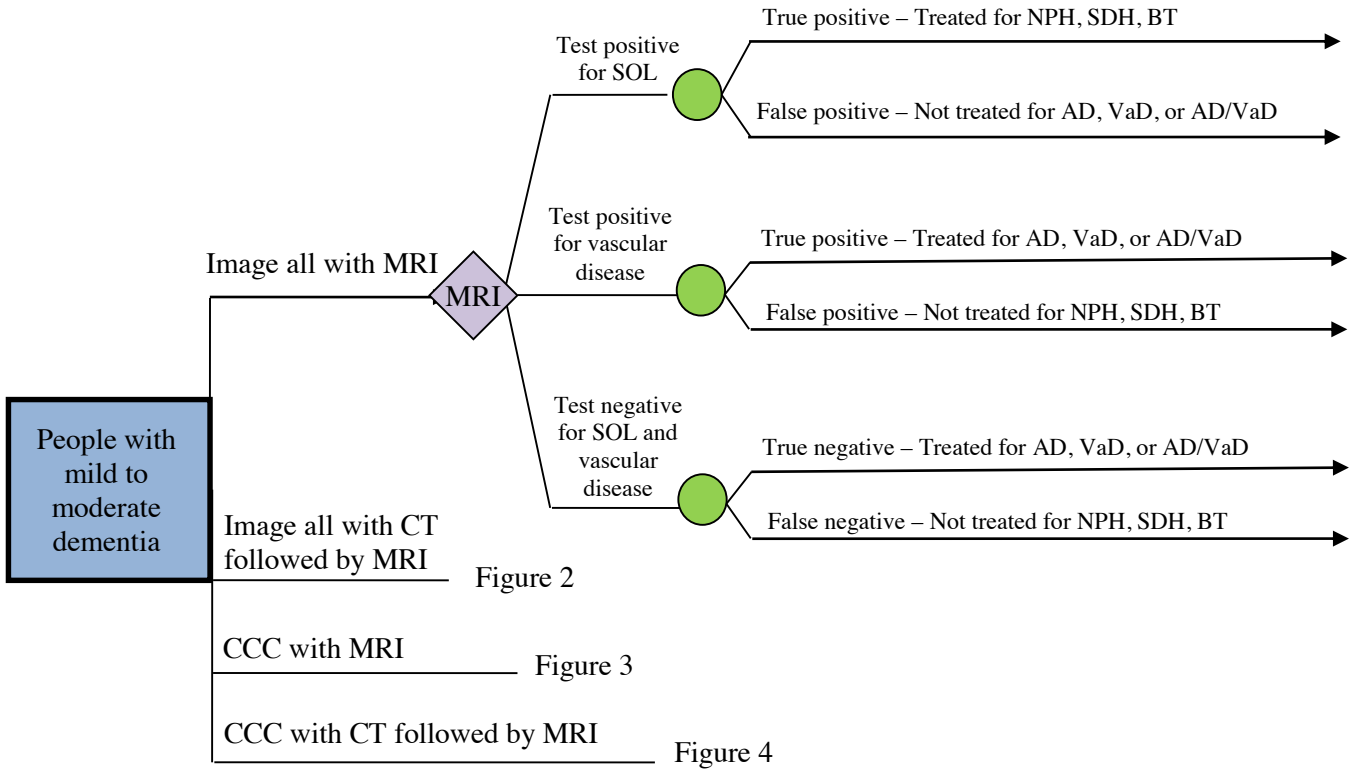

Figure 1: Schematic Structure of Diagnostic Strategy: Image All with MRI First

Abbreviations: AD, Alzheimer disease; BT, brain tumour; CCC, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia; CT, computed tomography; MRI, magnetic resonance imaging; NPH, normal-pressure hydrocephalus; SDH, subdural hematoma; SOL, space-occupying lesion; VaD, vascular dementia.

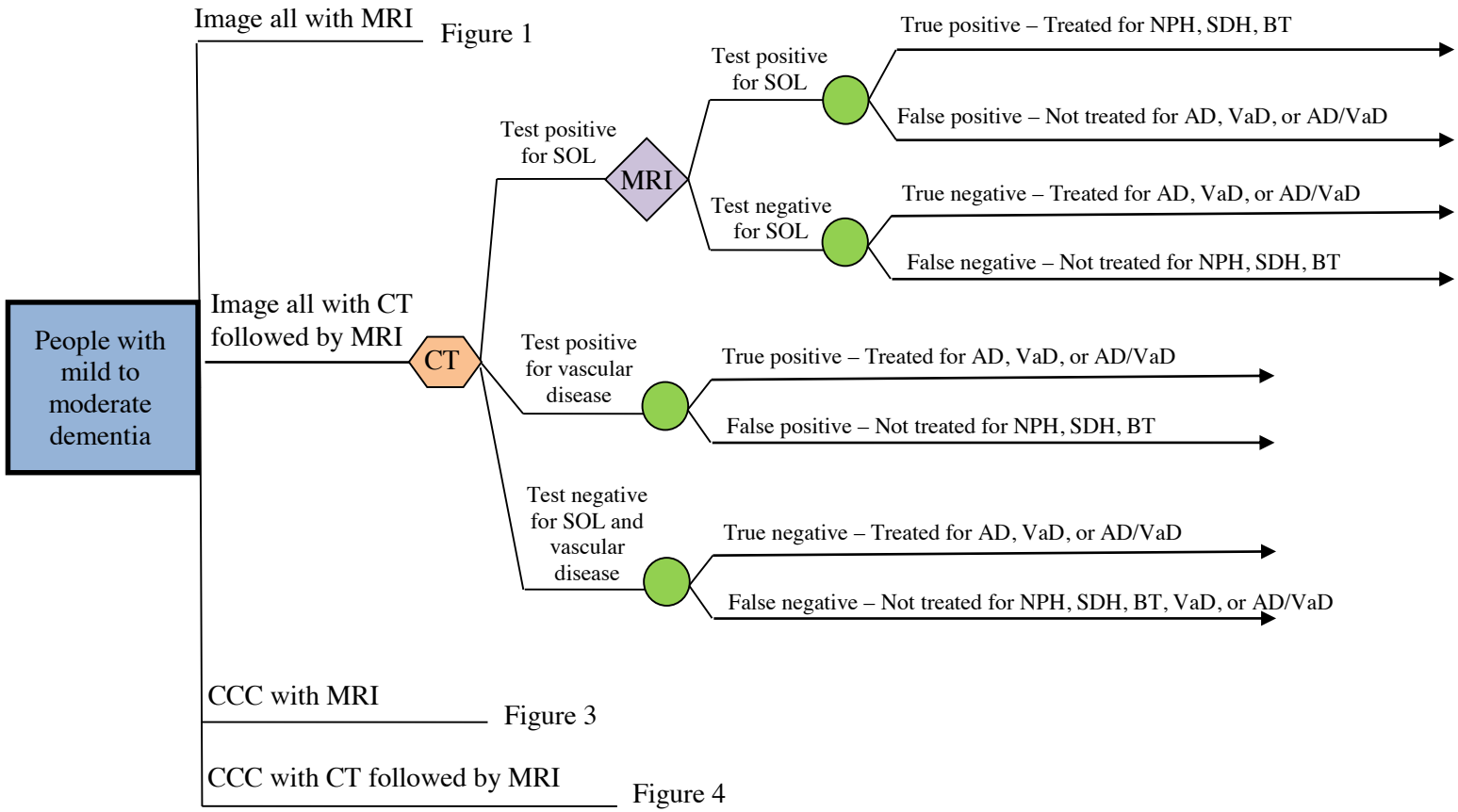

Figure 2: Schematic Structure of Diagnostic Strategy: Image All with CT First

Abbreviations: AD, Alzheimer disease; BT, brain tumour; CCC, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia; CT, computed tomography; MRI, magnetic resonance imaging; NPH, normal-pressure hydrocephalus; SDH, subdural hematoma; SOL, space-occupying lesion; VaD, vascular dementia.

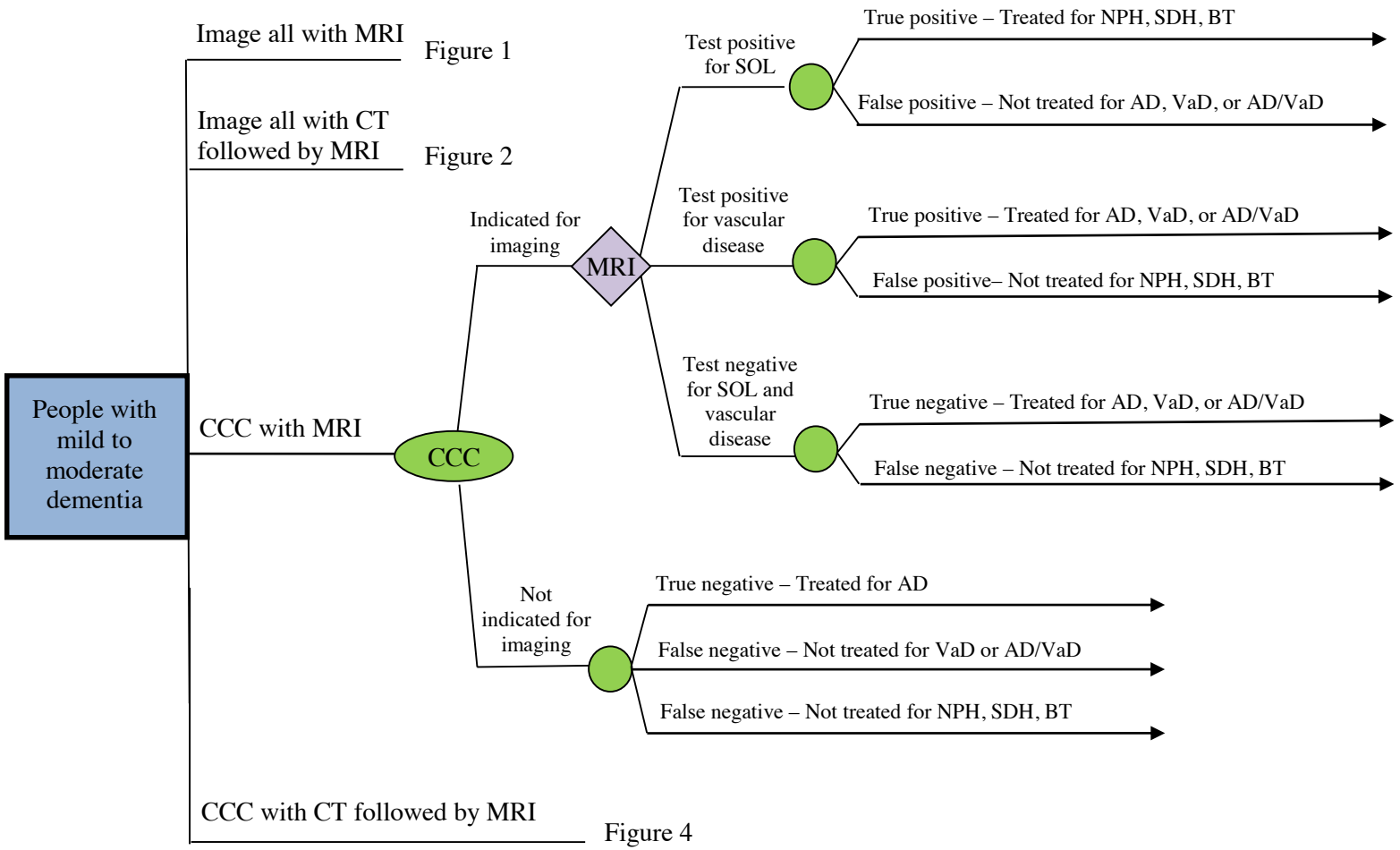

Figure 3: Schematic Structure of Diagnostic Strategy: CCC with MRI First

Abbreviations: AD, Alzheimer disease; BT, brain tumour; CCC, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia; CT, computed tomography; MRI, magnetic resonance imaging; NPH, normal-pressure hydrocephalus; SDH, subdural hematoma; SOL, space-occupying lesion; VaD, vascular dementia.

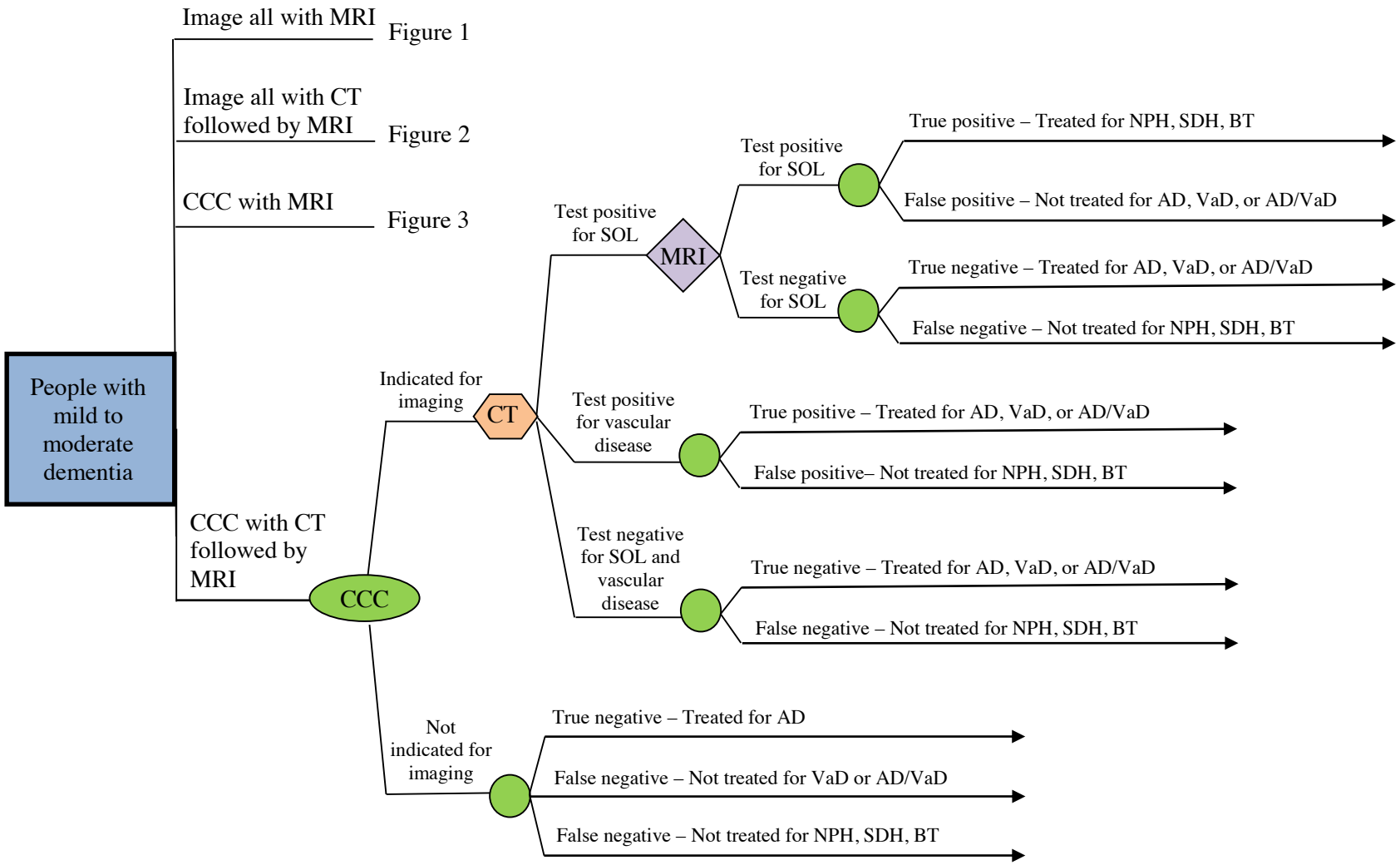

Figure 4: Schematic Structure of Diagnostic Strategy: CCC with CT First

Abbreviations: AD, Alzheimer disease; BT, brain tumour; CCC, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia; CT, computed tomography; MRI, magnetic resonance imaging; NPH, normal-pressure hydrocephalus; SDH, subdural hematoma; SOL, space-occupying lesion; VaD, vascular dementia.

Natural History, Treatment Efficacy, and Costs

Alzheimer Disease

Our approach to modelling the natural history of people with Alzheimer disease (AD) was informed by a systematic review of AD modelling methods by Green et al. (25) Of 42 published studies, 10 general modelling frameworks used to model AD were identified by the authors. Each used a different method to model the statistical relationship between risk factors and health states. The authors did not recommend one method over another; rather, they emphasized the importance of considering the particular requirements of a particular analysis when selecting structures and data. On this basis, we chose to use a cohort Markov model representing changes in disease state as transitions between severity stages. We also needed to consider the need for nursing home care in terms of either disease state or costs and quality of life.

The model developed by Neumann et al (17) was selected as the most appropriate for this analysis. Neumann et al (17) modelled AD over time using transition probabilities derived from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) database. The severity of cognitive decline was divided into mild, moderate, and severe health states according to the Mini-Mental State Examination (MMSE) score. From a possible score of 30, less than 10 was indicative of severe AD; 10 to 20 indicated moderate AD; and 21 to 26, mild AD. Figure 5 shows the basic structure of this model, with data sources and model modifications discussed below and summarized in Table 4.

Currently, 2 groups of drugs are licensed for symptomatic treatment of AD: acetylcholinesterase inhibitors (AChEIs, such as donepezil, galantamine, rivastigmine) and N-methyl-D-aspartate receptor antagonists (particularly memantine). Although there is no cure for AD, these drugs have been shown to slow symptomatic decline over trial periods of 12 to 24 months. According to data from available randomized controlled trials (RCT), donepezil reduced the risk of transition from mild to moderate AD by 50%. (26) Trials have not demonstrated a drug effect on the transition from moderate to severe AD, largely due to underpowered studies. Consistent with other models for the treatment of AD, it was assumed that donepezil also reduces the probability of transition to the severe health state by 50%. The effect of eliminating this assumption was tested in sensitivity analysis. The impact of side effects on costs and quality of life were not included in the model.

Two studies were identified that outline the costs associated with different stages of Alzheimer disease as measured by the MMSE. Costs reported by Hux et al (27) were used in preference to those reported by Herrmann et al (28) as they reported direct and indirect costs separately and included people living in nursing homes. Hux et al (27) used data from the Canadian Study of Health and Aging, a 1991–1992 survey of Canadians aged 65 or older, including a random sample of 9,008 living in the community and 1,225 living in long-term care. All costs were inflated to 2012 Canadian dollars. As noted by Hermann et al (28) treatment options for people with AD, including the availability of AChEIs, have changed since these data were collected. Therefore, we included the additional cost of donepezil and estimated that treatment would induce 2 extra physician visits in the first year and 1 in the second year for physicians to monitor the effectiveness of the drug, adequacy of the current dose, and presence of side effects. (17) Including the drug as an additional variable to the cost of care allowed the cost of treatment to be varied in sensitivity analysis.

Hux et al (27) reported average costs per patient for each disease state. This included costs attributed to patients living in the community and in long-term care facilities. The percentage of patients in each setting was reported for each group and adjusted for the Canadian population; these figures were used to adjust utility values. Therefore, rather than explicitly modelling the move from community to nursing homes for each stage of AD, we used average costs and utilities weighted to reflect these transitions.

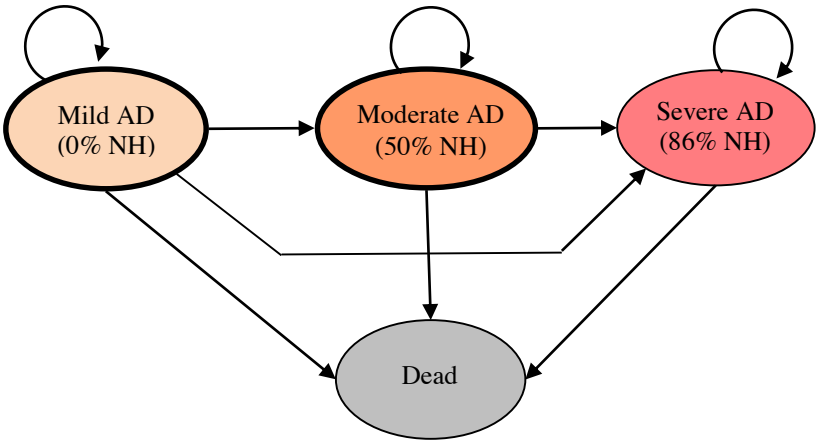

Figure 5: Schematic Diagram of Model Structure for Alzheimer Disease
Abbreviations: AD, Alzheimer disease; NH, nursing home.

Table 4: Natural History, Treatment Efficacy, and Costs of Alzheimer Disease

Model Parameter	Mean	Range	Source
Mild AD to moderate AD	32.3%	26.6%–38.3%	Neumann et al, 1999 (17)
Mild AD to severe AD	4.2%	5.0%–11.7%	Neumann et al, 1999 (17)
Mild AD to death	2.1%	0.0%–10.7%	Neumann et al , 1999 (17)
Moderate AD to severe AD	33.9%	28.1%–39.9%	Neumann et al, 1999 (17)
Moderate AD to death	5.3%	1.1%–12.5%	Neumann et al, 1999 (17)
Severe AD to death	15.3%	9.9%–21.6%	Neumann et al, 1999 (17)
Risk ratio for transition from mild to moderate AD	0.50	0.25–0.99	Neumann et al, 1999 (17)
Risk ratio for transition from moderate to severe AD	0.50	0.25–0.99	Neumann et al, 1999 (17)
Utility for mild AD (0% NH)	0.68	0.47–0.86	Neumann et al, 1999 (17)
Utility for moderate AD (50% NH)	0.51	0.37–0.65	Neumann et al, 1999 (17)
Utility for severe AD (86% NH)	0.32	0.16–0.50	Neumann et al, 1999 (17)
Cost of care for mild Alzheimer disease (0% NH)	$3,010	$2,449–$3,628	Hux et al, 1998 (27)
Cost of care for moderate Alzheimer disease (50% NH)	$24,393	$19,847–$29,401	Hux et al, 1998 (27)
Cost of care for severe Alzheimer disease (86% NH)	$43,582	$35,460–$52,529	Hux et al, 1998(27)
Annual cost of donepezil treatment	$1,811	$1,474–$2,183	Ontario Drug Benefit, 2013 (29)

Abbreviations: AD, Alzheimer disease; NH, nursing home.

Vascular Dementia (VaD) and Alzheimer Disease with Vascular Disease (Mixed Dementia)
Vascular dementia is the second most frequent cause of dementia, following Alzheimer disease. Although definitions vary across the literature, in general VaD describes several vessel disorders with different types of vascular lesions. (30) These lesions are often the result of ischemic or hemorrhagic stroke. Treatment aims to both improve dementia symptoms and control vascular risk factors.

One cost-effectiveness evaluation for the treatment of vascular dementia was identified in the literature. (31) However, effectiveness was assessed as unit decline using the cognitive subscale of the Alzheimer Disease Assessment Scale and the risk of adverse events over a 24-week time horizon. The natural history of the disease and long-term prognosis were not modelled or discussed. Therefore, an original model was developed with input from the expert panel. Figure 6 shows the basic structure of this model. The probabilities and costs used to inform the model are presented in Tables 5 and 6.

Ischemic stroke accounts for approximately 85% of all causes of stroke, (32;33) with a recurrence rate of 6% per year. (34) Recurrent stroke among survivors of hemorrhagic stroke occurs at a rate of approximately 4% per year. (35) Recurrent strokes were assumed to occur with the same incidence as in the baseline population (85% ischemic and 15% hemorrhagic). Overall, hemorrhagic stroke is associated with a higher risk of death compared with ischemic stroke. (36) It was assumed that people could only experience a single recurrent stroke event.

Aspirin and other antiplatelet agents are commonly prescribed by Canadian physicians for patients with VaD for the purpose of primary and secondary stroke prevention. (37) Because other antiplatelet agent agents have similar therapeutic benefit and a combination does not offer additional advantage, the effects observed in trials of aspirin were assumed to apply equally to these drugs.

To our knowledge, no studies have specifically evaluated the effectiveness of aspirin in people with vascular dementia. However, the effectiveness of aspirin for preventing secondary cardiovascular events among people with ischemic vascular disease is well-established. A meta-analysis of 16 placebo-controlled RCTs by the Antithrombotic Trialists' Collaboration found that aspirin reduced the risk of recurrent ischemic stroke by 22%. (38) This must be balanced against a 67% increased risk of hemorrhagic stroke in the same patients. (38) The absolute annual risk of baseline and adjusted treatment per patient is presented in Table 5.

Table 5: Annual Absolute Stroke Risk per Patient in Model Cohort

Original Stroke	Recurrent Stroke	Annual Risk Off Treatment		Annual Risk On Treatment		Baseline Risk, % (37% on Treatment)	Adjusted Risk, % (78% Ischemic and 18% Hemorrhagic on Treatment)
		%	Total, %	%	Total,%		
Ischemic (85% of cohort)	Ischemic	5.7	6.7	4.4	6.1	6.1	5.9
	Hemorrhagic	1.0		1.7			
Hemorrhagic (15% of cohort)	Ischemic	3.7	4.4	2.8	3.9		
	Hemorrhagic	0.7		1.1			

It was assumed that patients who were correctly diagnosed as having VaD or VaD/AD (true positive for those suspected of having a vascular cause of dementia) would be treated according to the results of the MRI, which would indicate either an ischemic or hemorrhagic cause of cerebrovascular stroke. The vast majority of patients with ischemic causes were assumed to receive aspirin, (37) and antiplatelet use was reduced by half (from the baseline prevalence of prescriptions) for those with hemorrhagic stroke. People who were not assessed or who were incorrectly diagnosed as *not* having a vascular cause of dementia (false negative) were assumed to be taking low-dose aspirin in accordance with the percentage of older people who regularly take the drug for cardiovascular protection in the general population. (39) Therefore, the advantage of correctly identifying a vascular cause of dementia was a reduced risk of stroke in those with both hemorrhagic and ischemic initial causes of stroke.

A longitudinal study by Bruandet et al (40) was used to inform symptomatic progression of VaD and mixed AD and VaD. (40) Ninety-five percent of patients in AD and mixed dementia groups and 36% of patients in the VaD group were receiving AChEI for the symptomatic treatment of dementia. Over an average follow-up of 4.7 years, it was found that mean cognitive function declines significantly more slowly in patients with VaD compared with those with AD. On average, MMSE declined by 2 points (±

2.5) every year in people with AD, 1.5 points (± 2.3) per year for people with mixed dementia, and 0.6 points (± 2.7) per year for people with VaD. Therefore, in the model it was assumed that people with mixed dementia and VaD transition between symptomatic states at a rate that is 25% and 70% less, respectively, than those with AD. People with VaD and mixed dementia also have a slightly lower risk of mortality compared with people with AD. (40)

The relationship between cardiovascular events and cognitive decline is complicated by the effect of the former on the latter. Each new stroke may be associated with a stepwise decline in cognitive function. In the model, stroke events were modelled independently of cognitive decline; it was assumed that the effect of these events on symptomatic decline would be captured by the Bruandet study. (40)

The costs associated with both index and follow-up care for people with each type of stroke was obtained from a 2005 Canadian study and inflated to 2012 dollars. (41) The quality of life experienced by patients with stroke was obtained from a study by Sullivan et al. (42) It was assumed that the utility for patients with ischemic and hemorrhagic stroke did not differ.

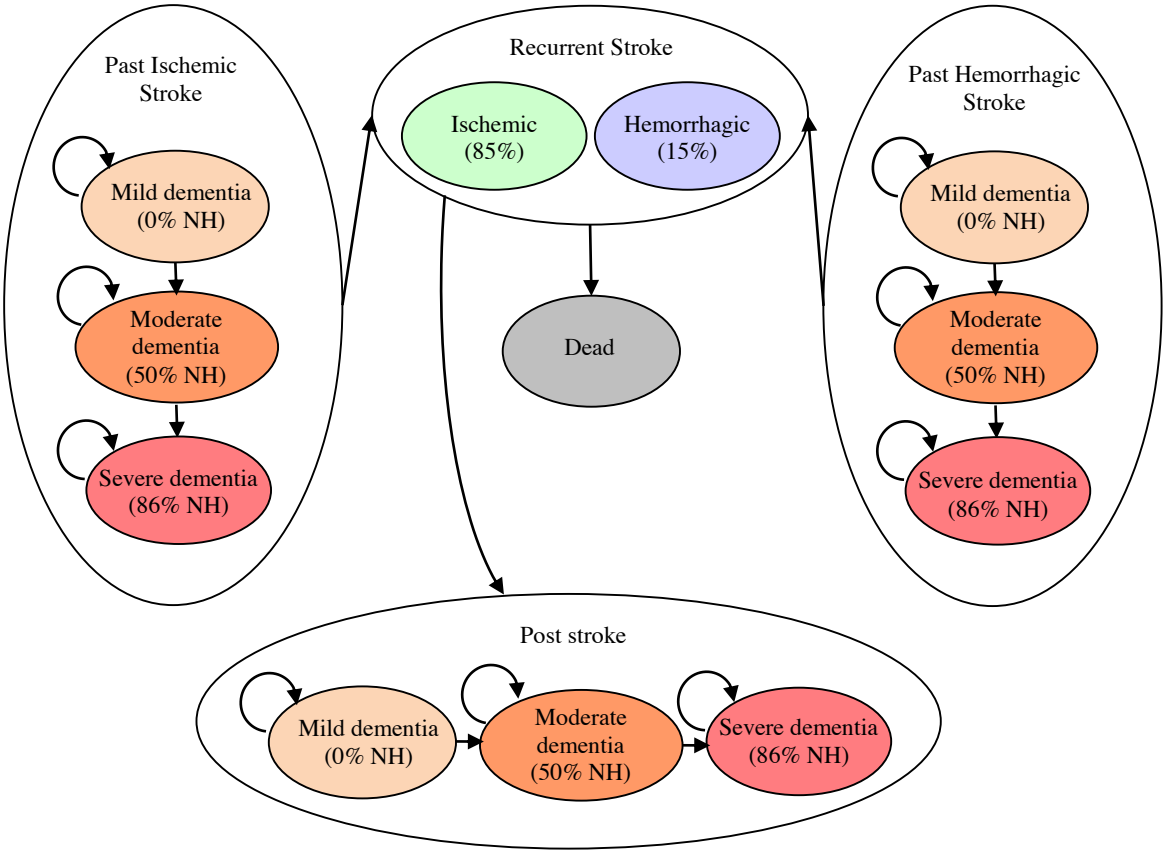

Figure 6: Schematic Diagram of Model Structure for Vascular and Mixed Dementia
Abbreviations: NH, nursing home.

Table 6: Natural History, Treatment Efficacy, and Costs of Vascular and Mixed Dementia

Model Parameter	Mean	Range	Source
Percentage of VaD caused by ischemic stroke	85%	65.0%–97.3%[a]	Rosamund et al, 2008 (33)
Percentage of VaD caused by hemorrhagic stroke	15%	12.2%–18.1%[a]	Rosamund et al, 2008 (33)
Probability of recurrent stroke in ischemic VaD	6.6%	7.7%–9.7%	Petty et al, 1998 (34)
Probability of recurrent stroke in hemorrhagic VaD	4.3%	3.5%–5.4%	Bailey et al, 2001 (35)
Proportion of recurrent strokes that are of the same type as original stroke in those with ischemic VaD	85%	65.0%–97.3%[a]	See text
Proportion of recurrent strokes that are of the same type as original stroke in those with hemorrhagic VaD	15%	12.2%–18.1%[a]	See text
90-day mortality following ischemic stroke	10.9%	8.9%–13.1%[a]	Andersen et al, 2009 (36)
90-day mortality following hemorrhagic stroke	25.0%	20.3%–30.1%[a]	Andersen et al, 2009 (36)
Percentage prescribed aspirin and other antiplatelet agents if diagnosed with ischemic stroke	78.0%	61.0%–91.1%[a]	Molnar et al, 1998 (37)
Percentage prescribed aspirin and other antiplatelet agents if diagnosed with hemorrhagic stroke	18.5%	14.1%–23.2%	Expert opinion
Percentage of the general elderly population who regularly take aspirin for general cardiovascular protection	37.0%	28.1%–46.3%	Juby et al, 2008 (39)
Relative risk of secondary ischemic stroke for people taking aspirin compared with placebo	0.78	0.61–0.99	ATC, 2009 (38)
Relative risk of secondary hemorrhagic stroke for people taking aspirin compared with placebo	1.67	0.97–2.90	ATC, 2009 (38)
Relative probability of progression from mild to moderate dementia for people with VaD vs. AD (35% on AChEI treatment)	75.4%	57.2%–96.5%	Bruandet et al, 2009 (40)
Relative probability of progression from mild to moderate dementia for people with mixed dementia vs. AD (95% on AChEI treatment)	30.1%	11.8%–57.1%	Bruandet et al, 2009 (40)
Relative risk of mortality in people with VaD vs. AD	0.70	0.50–1.10	Bruandet et al, 2009 (40)
Relative risk of mortality in people with mixed dementia (VaD with AD) vs. AD	0.70	0.50–1.00	Bruandet et al, 2009 (40)
Annual cost of aspirin (80 mg)	$100	$68–$138	Ontario Drug Benefit[a] (29)
Index cost of ischemic stroke	$22,115	$18,539–$26,002	Goeree et al, 2005 (41)
Annual cost of care for ischemic stroke	$32,255	$27,039–$37,924	Goeree et al, 2005 (41)
Index cost of hemorrhagic stroke	$15,106	$10,240–$20,903	Goeree et al, 2005 (41)
Annual cost of care for hemorrhagic stroke	$43,403	$29,421–$60,060	Goeree et al, 2005 (41)
Stroke index disutility	0.05	0.02–0.10	Sullivan et al, 2006 (42)
Poststroke disutility	0.05	0.02–0.10	Sullivan et al, 2006 (42)

Abbreviations: AChEI, acetylcholinesterase inhibitor; AD, Alzheimer disease; ATC, Antithrombotic Trialists' Collaboration; VaD, vascular dementia; vs., versus; NH, nursing home.

[a] Calculated by assuming a 10% standard error.

Normal-Pressure Hydrocephalus (NPH)

Insertion of a shunt to remove excess cerebrospinal fluid is the recommended treatment for people with NPH. The basic structure of this model was informed by a cost-utility analysis by Stein et al (43) and simplified by the elimination of delayed adverse events. Costs and transition probabilities were updated with data from more recent published literature. Based on conversations with the expert panel, it was assumed that approximately 90% of people correctly identified as having NPH would receive a ventricular shunt.

A systematic review of the natural history of NPH (44) identified 1 study that aimed to compare the outcome of shunt versus no shunt in people with NPH. (45) In contrast to earlier studies suggesting that only 29% of patients would benefit from shunting, (43) Razay et al (45) found that, at 4-month follow-up, most patients who had received a shunt (67%) showed moderate or marked improvement in cognitive function, while the remaining patients were unchanged. In the no-shunt group, most patients (57%) showed moderate or marked worsening. (45) It was assumed that patients who experienced an improvement following treatment had a quality of life equal to that of someone with mild dementia; those who deteriorated were assigned to the severe dementia health state; and those who remained unchanged were distributed according to baseline prevalence of mild and moderate dementia.

A recent study of operative outcomes by Kahlon et al (46) reported that 5-year mortality was similar for surgical (37%) and non-surgical (38%) patients with NPH. Peri-operative complications occur in approximately 3% of patients. (43) Although procedure-related complications may be delayed and there is risk that patients may require operative shunt revision, (43) as a necessary simplification we adopted a conservative approach and did not include delayed adverse events. This is consistent with the approach taken for SDH recurrent brain tumour. The cost of treatment for people with NPH was based on a study of an adult population by Del Bigio (47) and was assumed to include the cost associated with complications. The schematic model structure is illustrated in Figure 7. Probabilities and costs used to inform this model are reported in Table 7.

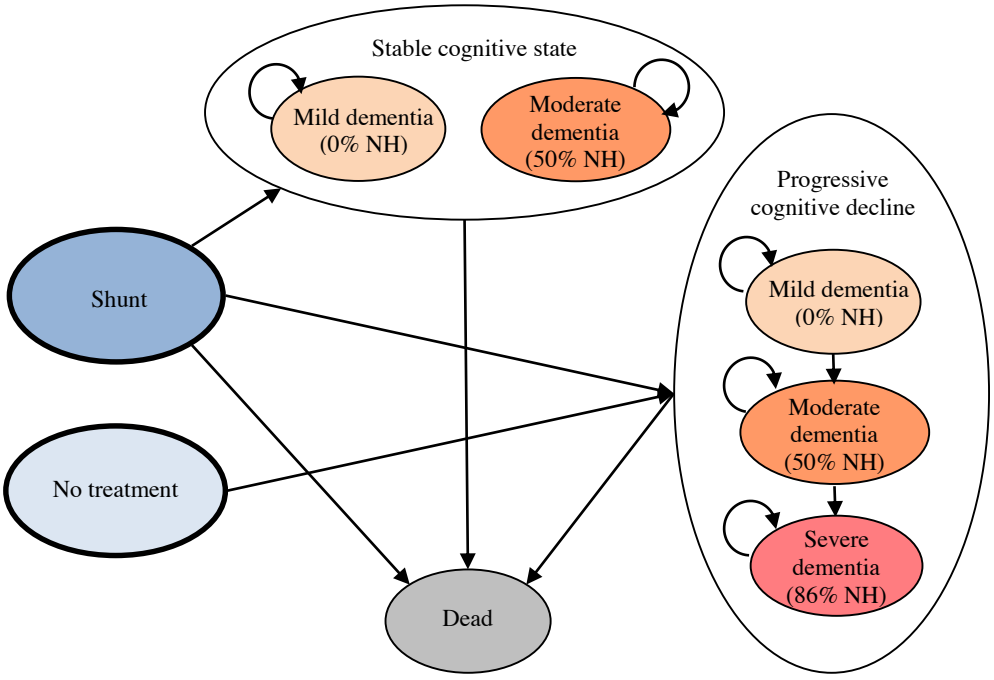

Figure 7: Schematic Diagram of Model Structure for Normal-Pressure Hydrocephalus

Abbreviations: NH, nursing home.

Table 7: Natural History, Treatment Efficacy, and Costs of Normal-Pressure Hydrocephalus

Model Parameter	Mean	Range	Source
Percentage of patients receiving shunt	90%	80%–100%	Expert opinion
Procedural complications	3.3%	2.7%–4.0%	Stein et al, 2006 (43)
Complication-related mortality	14.0%	12.6%–15.4%	Stein et al, 2006 (43)
Moderate or marked improvement following shunt (remainder experience no difference)	67%	44.4%–86.0%	Razay et al, 2009 (45)
Moderate or marked worsening following no shunt (remainder assumed to experience no difference)	57%	31.4%–80.7%	Razay et al, 2009 (45)
Annual mortality for patients receiving shunt	8.8%	0.1%–33.8%	Kahlon et al, 2007 (46)
Annual mortality for patients not receiving shunt	9.1%	0.1%–35.0%	Kahlon et al, 2007 (46)
Cost of ventricular shunt procedure	$21,708	$17,622–$26,124	Del Bigio, 1998 (47)

Subdural Hematoma (SDH)

The management of symptomatic patients with SDH typically includes surgical evacuation of the hematoma. In Canada, burr-hole craniotomy is the preferred technique for the initial management of SDH . (48) Although the majority of surgeons report that their management preference does not change with age, they also believe that the clinical status of their patient is an important factor in management. (48) In the model, it was assumed that approximately 80% of patients with correctly diagnosed SDH were suitable candidates for burr-hole craniotomy.

A widely cited review by Weigel et al (49) reported a mortality for SDH of 2.7%, morbidity of 3.8% and cure rate of 79.1%. However, the observation period for these outcomes was not specified, and the age of the population was much younger than that included in the model. More recent retrospective reviews of elderly patients found that 6.1% experience peri-operative complications (50) and 16.7% died in hospital. (51)

Following surgery, patients' neurological status has been shown to improve, with 83% of patients achieving a good outcome after surgery. (50) In the absence of comparative evidence of neurological status for those who did not undergo surgery, it was assumed that the proportion of patients who are untreated for SDH and experience worsening symptoms is the same as for NPH. (45) Over 5 years, the probability of death for people who underwent surgery and for those who did not receive treatment was estimated at 40% and 75%, respectively. (51)

The cost of treating subdural hematoma was based on 2011 inpatient costs (age ≥ 70 years) reported by the Ontario Case Costing Initiative, (52) inflated to 2012 Canadian dollars. It was assumed that the cost of complications would be included in this overall estimate.

Consistent with our approach to modelling NPH and BT, long-term health utilities and costs of care for SDH were correlated with the degree of dementia. It was assumed that patients who experience an improvement achieve a health status similar to those with mild AD and maintain this health state over the long term. Those who deteriorate were assumed to progress to a health state comparable to people with severe AD. Similarly, it was assumed that patients who were not correctly diagnosed or not treated were assigned utility, costs, and rates of disease progression according to the baseline distribution of patients with untreated mild to moderate AD. The schematic model structure is illustrated in Figure 8. Probabilities and costs used to inform this model are reported in Table 8.

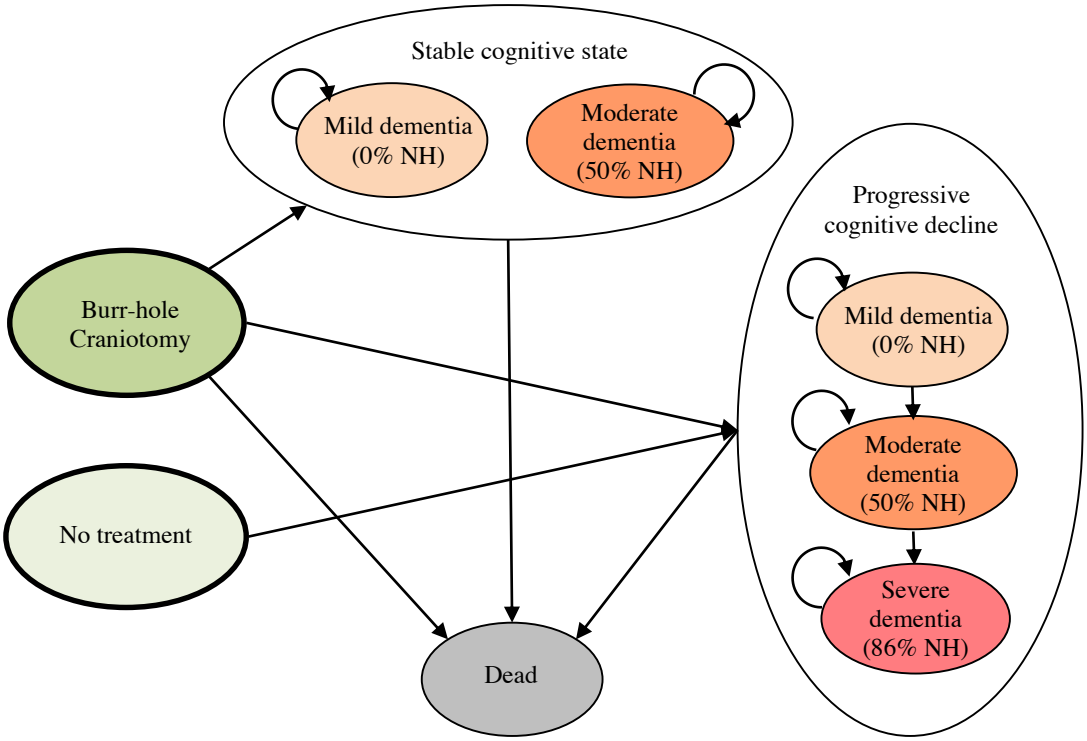

Figure 8: Schematic Diagram of Model Structure for Subdural Hematoma

Abbreviations: NH, nursing home.

Table 8: Natural History, Treatment Efficacy, and Costs of Subdural Hematoma

Model Parameter	Mean	Range	Source
Percentage of patients receiving treatment	80%	70%–90%	Expert opinion
Procedural complications	6.1%	3.4%–11.0%	Borger et al, 2012 (50)
Procedure-related mortality	16.7%	12.0%–23.3%	Miranda et al, 2011 (51)
Improvement following craniotomy (remainder assumed to experience no difference)	83.0%	76.6%–88.6%	Borger et al, 2012 (50)
Worsening following no treatment (remainder assumed to experience no difference)	57%	31.4%–80.7%	Razay et al, 2009 (45)
5-year mortality for treated patients	40.0%	Not reported	Miranda et al, 2011 (51)
5-year mortality for people not treated	74.0%	Not reported	Miranda et al, 2011 (51)
Cost of treating subdural hematoma	$9,298	$7,325–$11,501	Ontario Case Costing Initiative, 2011 (52)

Brain Tumour (BT)

Cognitive dysfunction is a common initial symptom of brain tumours. In the age group represented in our model, approximately 87% of primary brain tumours are malignant. (13) For the purpose of this model, treatment options and outcomes for malignant tumours were obtained from literature relating to gliomas, the most common form of malignant tumour in the elderly. Data used to inform the natural history and treatment outcomes for benign tumours was based on research conducted in elderly people with meningioma. The natural history, treatment outcomes, and costs for both types of tumour are summarized in the text below and in Tables 9 to 11. Based on these data, overall probability of treatment, mortality, and cost were calculated in Excel using probabilistic simulation and reported in Table 11. These global estimates were used to inform parameters in the model developed in TreeAge. The model structure is illustrated in Figure 9.

Malignant Primary Brain Tumour

Current treatment options for people with glioblastoma consist of resection of the tumour, radiotherapy, and chemotherapy. However, a large proportion of patients are ineligible or unwilling to undergo these treatments. An American population-based study of elderly people with glioblastomas found that surgical resection was performed in 61% of patients at the time of diagnosis. (53) Thirty-day mortality for elderly patients undergoing craniotomy for primary metastatic brain tumours is approximately 4%. (54)

Adjuvant chemo-radiation therapy consisting of temozolomide (150–200mg/m^2) is considered the standard of care following surgery for patients with newly diagnosed glioblastoma. (55) The same United States study found that, within 3 months of diagnosis, 55% of elderly patients received only radiotherapy, 10% received radiotherapy and chemotherapy, and 34% did not receive either. (55) As less than 1% received only chemotherapy, this alternative was not included in our model. In the absence of available Canadian evidence—one Canadian study (56) was identified but the expert panel considered it out of date—it was assumed that treatment patterns in Ontario are the same as in the United States study. (54)

Treatment outcomes for each group were obtained from a retrospective review of people with newly diagnosed glioblastoma and a mean age of 71 years. (57) Treatment groups were divided according to those receiving resection alone, resection plus radiotherapy (2 Gy per fraction once daily for 5 days per week over 6 weeks), and resection plus radiotherapy and chemotherapy (temozolomide 150–200 mg/m^2 according to standard 5-day schedule every 28 days). The annual probability of mortality was calculated based on reported median survival for each group. It was assumed that patients who do not undergo treatment have an average survival of less than 1 year. (58)

Studies have found that there is no change in quality of life or cognitive function between groups receiving resection and/or radiotherapy compared with best supportive care. (57;59) Therefore, average baseline quality of life was assigned to treated patients based on the baseline distribution of mild to moderate dementia. Those with untreated brain tumours were assumed to decline at the same rate as those with AD, although with a much shorter life expectancy.

The total cost of each treatment strategy was obtained from a Nova Scotia study that evaluated the direct cost of patients with malignant glioma from the time of diagnosis to death. (60) Because the majority of costs were incurred within the initial treatment phase (including hospitalization and surgery), total treatment costs were applied only to the first cycle of the model. All costs were inflated from 1998 to 2012 Canadian dollars. It was assumed that patients who did not receive treatment incurred the cost of an MRI for the purpose of diagnosis and staging.

Table 9: Natural History, Treatment Efficacy, and Costs of Malignant Primary Brain Tumour

Model Parameter	Mean	Range	Source
Patients with glioblastoma or astrocytoma	87.0%	80.6%–92.3%	Simon and Lubin, 1985 (13)
Surgical resection at diagnosis	61.5%	59.6%–63.4%	Iwamoto et al, 2008 (53)
Surgical mortality	4.3%	1.6%–8.3%	Seicean et al, 2013 (54)
No resection at diagnosis	38.5%	36.1%–40.9%	Iwamoto et al, 2008 (53)
Radiotherapy + chemotherapy within 3 months	9.8%	7.1%–12.9%	Iwamoto et al, 2008 (53)
Radiotherapy within 3 months	56.0%	53.9%–58.0%	Iwamoto et al, 2008 (53)
No further treatment	34.5%	32.0%–37.0%	Iwamoto et al, 2008 (53)
No treatment: 1-year mortality	100.0%	Fixed	Ewelt et al, 2011 (57)
Resection only: 1-year mortality	99.0%	94.2% –100.0%	Ewelt et al, 2011 (57)
Resection + RT: 1-year mortality	84.3%	71.1%–93.9%	Ewelt et al, 2011 (57)
Resection + RT + CHX: 1-year mortality	42.6%	26.1%–60.1%	Ewelt et al, 2011 (57)
Total cost of patients undergoing resection only	$16,319	$13,511–$19,389	Mendez et al, 2001 (60)
Total cost of patients undergoing resection + RT	$24,971	$20,517–$29,792	Mendez et al, 2001 (60)
Total cost of patients undergoing resection + RT + CHX	$30,729	$26,361–$35,427	Mendez et al, 2001 (60)
Total cost of patients with no treatment	$880	$712–$1,065	Ontario Case Costing Initiative, 2011 (52)

Abbreviations: CHX, chemotherapy; RT, radiotherapy.

Benign Primary Brain Tumour

Meningiomas are generally slow-growing and benign. For patients with surgically accessible tumours, surgical intervention is recommended when the tumour begins to cause symptoms or displays significant growth on consecutive CT or MRI images. (61) Other patients with surgically inaccessible tumours or who are not otherwise eligible for surgery may be treated with stereotactic radiosurgery. (61) A recent American population-based study of people with benign meningiomas reported that initial treatment included partial or total resection in 43% of patients and either biopsy or no treatment in the remainder. (62) Nine percent of patients later received radiotherapy. (62)

Surgical mortality for elderly patients undergoing resection is approximately 6%. (63) Limited data are available to inform the long-term survival of elderly patients treated with resection or radiotherapy or for those receiving no treatment. Based on reviews by Cahill and Claus, (62) 5-year survival for people undergoing resection alone was estimated at 50%, and it was assumed that the additional use of stereotactic radiotherapy reduces the risk of mortality by half compared to resection alone and that no treatment increases the risk by half.

A comparison of elderly patients' pre- and postoperative cognitive function revealed no significant deterioration. (64) Therefore, it was assumed that patients maintain their preoperative quality of life. In the absence of other data, it was assumed that the cost of treatment for patients with meningioma was the same as for patients with glioma undergoing similar methods of treatment.

Table 10: Natural History, Treatment Efficacy, and Costs of Benign Primary Brain Tumour

Model Parameter	Mean	Range	Source
Patients with benign meningioma	13.0%	7.7%–19.4%	Simon and Lubin, 1985 (13)
Surgical resection at diagnosis	44.6%	43.7%–45.5%	Cahill and Claus, 2011 (62)
Biopsy or no resection at diagnosis	55.4%	54.5%–56.3%	Cahill and Claus, 2011 (62)
Surgical mortality	5.6%	1.2%–13.0%	Konglund et al (63)
Radiotherapy	8.9%	8.4%–9.5%	Cahill and Claus, 2011 (62)
No further treatment	91.1%	90.5%–91.6%	Cahill and Claus, 2011 (62)
No treatment: 1-year mortality	5.6%	4.5%–6.7%	Expert opinion
Resection: 1-year mortality	12.9%	10.5%–15.6%	Expert opinion
Resection + radiotherapy: 1-year mortality	24.2%	19.6%–29.1%	Expert opinion
Total cost of patients undergoing resection only	$16,319	$13,511–$19,389	Mendez et al, 2001 (60)
Total cost of patients undergoing resection + RT	$24,971	$20,517–$29,792	Mendez et al, 2001 (60)
Total cost of patients with no treatment	$880	$712–$1,065	Ontario Case Costing Initiative, 2011 (52)

Abbreviations: RT, radiotherapy.

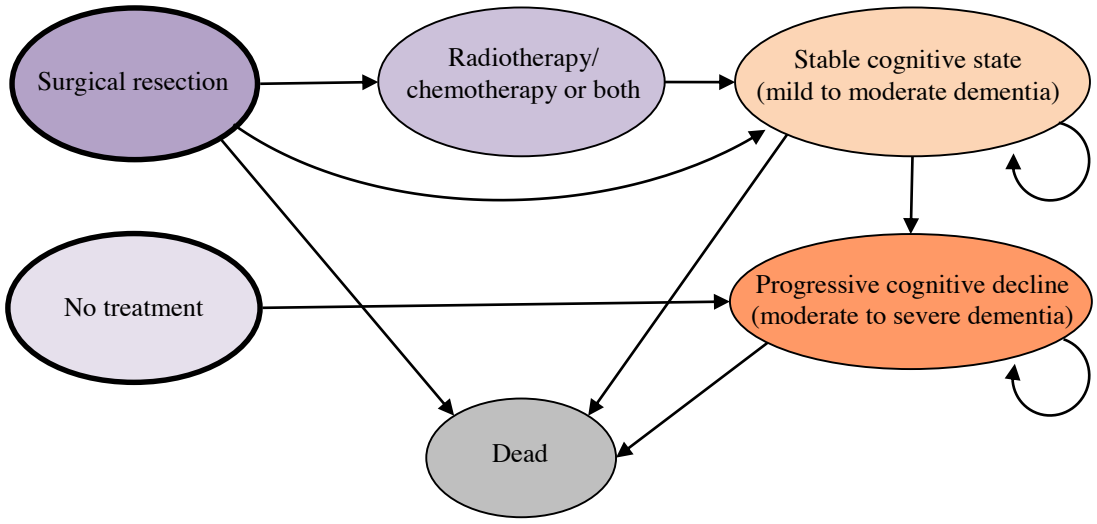

Figure 9: Schematic Diagram of Model Structure for Brain Tumour

Table 11: Overall Transition Probabilities and Costs of Primary Brain Tumour

Model Parameter	Mean	Range	Source
Average probability of resection	59.4%	57.7%–60.1%	Weighted means calculated by Monte Carlo analysis based on data presented in Tables 9 and 10
Average surgical mortality	4.5%	1.9%–8.0%	
Average1-year mortality for patients not treated	86.9%	80.0%–92.3%	
Average 1-year mortality for patients treated	46.3%	40.5%–51.6%	
Average cost of no treatment	$880	$712–$1,065	
Average cost of treatment	$13,276	$11,367–$15,101	

Model Parameters

Prevalence

The prevalence of each condition in the baseline population is reported in Table 12. The prevalence of potentially treatable and neurodegenerative causes of dementia are needed to determine the absolute number of true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN). Based on a systematic literature review by Clarfeld et al, (22) the prevalence of potentially reversible dementia in the community was estimated at 4.2% (95% CI, 3.0%–5.5%). The prevalence of each of the 3 most common causes of SOLs reported by Clarfield (22) was used to inform the relative probability of SDH, NPH and BT.

Based on recent published findings, the expert panel believed the relative prevalence of AD, VaD, and VaD/AD of community-dwelling adults with dementia (65) was used in preference. In sensitivity analysis, we explored the effect that an increased prevalence observed in tertiary care centres would have on the results of the model.

Table 12: Prevalence of Treatable and Neurodegenerative Causes of Dementia in the Community

Model Parameter	Mean, %	Range, %	Source
Space-occupying lesions	4.2	3.0–5.5	Clarfield, 2003 (22)
Subdural hematoma (SDH)	36.5	21.2–62.0	Clarfield, 2003 (22)
Normal-pressure hydrocephalus (NPH)	32.7	17.7–57.8	Clarfield, 2003 (22)
Brain tumour (BT)	30.8	16.0–55.5	Clarfield, 2003 (22)
Neurodegenerative causes of dementia	95.8	94.5–97.0	Clarfield, 2003 (22)
Alzheimer disease (AD)	63.3	59.1–67.5	Feldman et al, 2003 (65)
Alzheimer disease and vascular dementia (AD/VaD)	25.1	21.3–28.9	Feldman et al, 2003 (65)
Vascular dementia (VaD)	11.6	9.0–14.6	Feldman et al, 2003 (65)

Diagnostic Accuracy

To evaluate the diagnostic accuracy of the prediction rule and imaging modality, the probability of obtaining a positive and negative test result and the probability that these results truly represent the presence or absence of disease must be calculated. Differences in the sensitivity and specificity of each prediction rule and imaging modality were based on the results of the EBA. In studies assessing the diagnostic accuracy of each clinical prediction rule, sensitivity was defined as the proportion of patients with a potentially reversible cause of dementia who were correctly identified as such. Specificity referred

to the proportion of patients with an irreversible cause of dementia who were correctly identified. In studies assessing the diagnostic accuracy of CT and MRI, sensitivity was defined as the proportion of patients correctly identified as having cerebrovascular changes, while specificity referred to the proportion of patients correctly identified as having noncerebrovascular changes.

The probability of a positive and negative test result can be derived from the pretest probability of the disease (prevalence) and the sensitivity and specificity of the test using Bayes' theorem, (66) where P is probability, T+/- means test is positive/negative, and D+/- is disease present/absent:

$$P(T+) = P(T+ \mid D+)\, P(D+) + P(T+ \mid D-)\, P(D-);$$
$$P(T-) = 1-P(T+);$$
$$PPV = P(T+ \mid D+)\, P(D+) \;/\; P(T+); \text{ and}$$
$$NPV = P(T- \mid D-)\, P(D-) \;/\; P(T-)$$

When one diagnostic test precedes the use of another, the baseline prevalence of a condition must be adjusted to account for the post-test probability of an individual having the condition of interest. The post-test probability can be calculated using the likelihood ratio (LR) for the test, which is calculated from the sensitivity and specificity of the test and therefore does not depend on prevalence in the reference group:

$$\text{Positive post-test probability} = (P(D+) / P(D-) \times LR+) / [\, (P(D+) / P(D-) \times LR+) + 1 \,]$$

The sensitivity and specificity of the CCC guideline was obtained from a study by Sitoh et al (21) in which the medical records of 210 patients with mild to moderate dementia were reviewed to extract relevant clinical variables. Based on these variables, patients were classified as being eligible or ineligible for neuroimaging according to the CCC guidelines. All patients had undergone CT scanning. A neuroradiologist reviewed the CT brain scans of all the above patients and evaluated them for the presence of space-occupying lesions (NPH, SDH, and BT) and strokes (small vessel infarcts or lacunes, large vessel infarcts, and white matter lesions) (Table 13). The sensitivity and specificity of the guideline were then calculated in terms of the presence or absence of SOLs (Table 14) and strokes (Table 15).

Table 13: Utility of CCC Clinical Prediction Rules

Total N	Scans Indicated	SOLs Detected	Strokes Detected	Scans Avoided	SOLs Missed	Strokes Missed
210	166	7	94	44	0	26

Abbreviations: CCC, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia; SOL, space-occupying lesion.
Source: Sitoh et al, 2006. (21)

Table 14: Sensitivity and Specificity of CCC for Diagnosis of Space-Occupying Lesions

		CT Outcome		
		Test Positive	**Test Negative**	
CCC Outcome	Test positive for neuroimaging	7 (TP)	159 (FP)	**PPV = 5.3% (95% CI, 3.8%–6.9%)**
	Test negative for neuroimaging	0 (FN)	44 (TN)	**NPV = 99.8% (95% CI, 99.7%–99.9%)**
		Sensitivity = 100.0% (95% CI, 59.0%–100%)	**Specificity = 21.7% (95% CI, 16.2%–28.0%)**	Total N = 210

Abbreviations: CCC, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia guidelines; CT, computed tomography; FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

Table 15: Sensitivity and Specificity of CCC for Diagnosis of Vascular Causes of Dementia

		CT Outcome		
		Test Positive	**Test Negative**	
CCC Outcome	Test positive for neuroimaging	94 (TP)	72 (FP)	**PPV = 34.7% (95% CI, 30.1%–39.5%)**
	Test negative for neuroimaging	26 (FN)	18 (TN)	**NPV = 62.9% (95% CI, 52.6%–72.4%)**
		Sensitivity = 78.3% (95% CI, 72.5%–83.6%)	**Specificity = 20.0% (95% CI,14.9%–25.7%)**	Total N = 210

Abbreviations: CCC, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia guidelines; CT, computed tomography; FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

Proportion of Patients Eligible for Neuroimaging According to CCC Guidelines

The probability that a patient was eligible for neuroimaging according to the CCC guidelines was calculated using the combined prevalence of SOL and vascular dementia (VaD and AD/VaD) and the sensitivity and specificity of the CCC guidelines for the diagnosis of these conditions. According to these data, 79% of the people with mild to moderate dementia met criteria for imaging and 21% did not (Table 16).

Table 16: Diagnostic Accuracy of CCC for Detecting VaD and SOL

Parameter	Mean, %	95% CI
Prevalence of SOL, VaD, and VaD/AD	**39.3**	**36.3–42.2**
Prevalence of AD	60.7	60.7–63.7
Sensitivity (probability of a positive test given disease is present)	**79.0**	**70.9–85.8**
Specificity (probability of a negative test given disease is not present)	**20.9**	**12.9–31.0**
Probability of a positive test (patient is eligible for imaging)	79.0	72.5–84.9
Probability of a negative test (no imaging)	21.0	15.1–27.5

Abbreviations: AD, Alzheimer disease; CCC, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia guidelines; CI, confidence interval; SOL, space-occupying lesions, VaD, vascular dementia.

Negative Predictive Value of CCC for Detecting Vascular and Treatable Dementia

The ability of the CCC guidelines to exclude patients with potentially treatable and vascular causes of dementia is estimated by calculating the NPV. Therefore, of the total cohort, 0.9% (equal to 21% x [100% – 95.8%]) are at risk of being misdiagnosed for SOL and 7.4% (21% x [100% – 64.7%]) for vascular disease.

Potentially Treatable Causes of Dementia

Diagnostic Accuracy of CT and MRI for Potentially Treatable Causes of Dementia

The clinical EBA did not identify any studies reporting the sensitivity and specificity of MRI and CT for the diagnosis of potentially treatable causes of dementia. Following discussions with the expert panel, several sources were used as proxy for the accuracy of these modalities for detecting BT and NPH. It was assumed that CT and MRI were equally accurate for detecting SDH. In the model, overall sensitivity and specificity were calculated according to the relative prevalence of each disease in the population (Table 17).

Table 17: Diagnostic Accuracy of MRI and CT for Detecting Space-Occupying Lesions

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Source
Brain Tumour			
MRI	92.0 (82.0–100.0)	99.0 (81.0–100.0)	Medina et al, 2001 (67) and expert opinion
CT	71.0 (55.0–90.0)	82.0 (62.0–90.0)	Medina et al, 2001 (67) and expert opinion
Normal-Pressure Hydrocephalus			
MRI	86.0 (65.2–98.0)	96.0 (82.3–100.0)	Ivkovic et al, 2013 (68) and expert opinion
CT	70.0 (45.5–89.5)	80.0 (57.2–95.3)	Ivkovic et al, 2013 (68) and expert opinion
Subdural Hematoma			
MRI	100.0 (fixed)	100.0 (fixed)	Expert opinion
CT	100.0 (fixed)	100.0 (fixed)	Expert opinion
Overall[a]			
MRI	**88.9 (61.3–100.0)**	**91.9 (65.2–100.0)**	See text
CT	**80.1 (52.6–100.0)**	**85.4 (57.5–100.0)**	See text

Abbreviations: CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging.
[a]Calculated according to baseline prevalence of each condition.

Post-Test Probability of Space-Occupying Lesions

By definition, the prevalence of SOL in the group deemed eligible for imaging according to the CCC guidelines is likely to differ from prevalence in the baseline population. The post-test probability of potentially treatable causes of dementia for patients undergoing the CCC strategy was calculated according to baseline prevalence and the sensitivity and specificity of the CCC guideline. This value was then used to inform the pretest probability of potentially treatable causes of dementia for patients undergoing CT and MR imaging. Patients in the image-all strategy presented for imaging with the prevalence of potentially treatable causes of dementia observed in the baseline cohort.

The model assumed that if patients test positive for SOL according to CT, they then receive MRI. This probability of testing positive was calculated according to the pre- or post-test prevalence of SOL and the sensitivity and specificity of CT for the diagnosis of these conditions.

Diagnostic Utility of Each Strategy

The ability of CT and MRI to exclude patients with potentially treatable and vascular causes of dementia is estimated by calculating the negative predictive value for patients who test negative according to each strategy.

For patients in the image-all strategy, the probability of testing positive via MRI will depend on whether or not they have first been imaged using CT. Having had a CT scan increases the probability of testing positive for a potentially treatable cause of dementia. However, this comes at the expense of a 15.2% probability of false negative diagnosis with CT [82.2% x (1 – 81.4%)] compared with 9.2% for MRI [88.7% x (1 – 89.6%)]. For patients in each of the CCC strategies, the risk of a false positive diagnosis

following CT and MRI is slightly lower due to the increased pretest probability as a result of the prediction rule.

Vascular Dementia

Post-Test Probability of Vascular Dementia

Patients who tested positive according to CCC guidelines (79%) were deemed eligible for neuroimaging. By definition, the prevalence of vascular dementia in this group is likely to differ from that in the baseline population. Therefore, the CCC post-test probability was calculated according to the sensitivity and specificity of the CCC guideline. This value was then used as the pretest probability of vascular dementia for patients undergoing CT and MR imaging. Patients in the image-all strategy presented for imaging with the prevalence of vascular dementia observed in the baseline cohort.

Diagnostic Accuracy of CT and MRI for Detecting Vascular Causes of Dementia

A recent systematic review and meta-analysis of CT compared with MRI for the diagnosis of vascular dementia was used to inform estimates of diagnostic accuracy. (23) Included studies evaluated each modality against clinical assessment (NINCDS-ADRDA, DSM-III, and ICD-10) with or without imaging. The results of this analysis suggested that MRI may be more accurate than CT for distinguishing VaD or VaD/AD from AD and other conditions. However, confidence intervals were wide with considerable heterogeneity between studies. The summary sensitivity and specificity of CT and MRI for detecting white matter lesions is reported in Table 18.

Table 18: Specificity and Sensitivity of MRI and CT for Detecting Vascular Causes of Dementia

Modality	Mean, %	95% CI
MRI		
Sensitivity (probability of a positive test given disease is present)	71.0	53.0–83.0
Specificity (probability of a negative test given disease is not present)	55.0	44.0–66.0
CT		
Sensitivity (probability of a positive test given disease is present)	95.0	87.0–98.0
Specificity (probability of a negative test given disease is not present)	26.0	12.0–50.0

Abbreviations: CI, confidence interval; CT, computed tomography, MRI, magnetic resonance imaging.
Source: Beynon et al, 2012. (21)

Cost of Imaging

The cost of CT and MRI was obtained from the Ontario Case Costing Initiative database, (52) which calculates the cost of treatment reported by 37 participating hospitals in the province. Values for MRI and CT with no contrast were obtained for people age 70 years and older. All costs were inflated to 2012 Canadian dollars (Table 19).

Table 19: Cost of MRI and CT in Ontario

Cost per Case	CT	MRI
Direct costs[a] ($ [SD])	388 (275)	644 (407)
Indirect costs[b] ($ [SD])	129 (90)	236 (150)
Total cost ($ [SD])	**517 (355)**	**880 (548)**

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; SD, standard deviation.
[a]Direct costs are directly related to the provision of care to the patient and include nursing (including operating room, ICU), diagnostic imaging, pharmacy, and laboratory.
[b]Indirect costs are overhead expense related to the running of hospitals, such as administration, finance, human resources, and plant operations.
Source: Ontario Case Costing Initiative, 2011. (52)

Quality of life

In cost-utility analyses, measures of health benefit are valued in terms of QALYs. The QALY is a measure of a person's length of life weighted by a valuation of their quality of life over that period. The weighting comprises 2 elements: the description of changes in quality of life and an overall valuation of that description. This valuation is referred to as a utility.

Disease progression and treatment effect were modelled in terms of their impact on cognitive function and institutionalization. For each natural history model, progression from mild, moderate, and severe dementia was modelled based on transition probabilities and health state utilities described by Peter Neumann et al based on CERAD data. (17) To simplify the model structure and include Canadian costs of AD, as reported by Hux et al, (27) global utilities for each severity state were calculated probabilistically in Excel according to the proportion of patients in each heath state who were in nursing homes in Canada (also based on Hux et al). Original and simulated values are reported in Table 20.

Table 20: Utilities

Health State	Mean	Range[a]	Source
Reported values			
Mild dementia (community)	0.68	0.47– 0.86	Neumann et al, 1999 (17)
Moderate dementia (community)	0.71	0.50–0.88	Neumann et al, 1999 (17)
Severe dementia (community)	0.54	0.34–0.73	Neumann et al, 1999 (17)
Mild dementia (nursing home)	0.48	0.29–0.68	Neumann et al, 1999 (17)
Moderate dementia (nursing home)	0.37	0.19–0.57	Neumann et al, 1999 (17)
Severe dementia (nursing home)	0.31	0.13–0.52	Neumann et al, 1999 (17)
Adjusted values			
Mild (0% nursing home)	0.62	0.47–0.86	Derived based on values reported above, using probabilistic Monte Carlo simulation
Moderate (50% nursing home)	0.53	0.37–0.65	
Severe (86% nursing home)	0.38	0.16–0.50	

[a]Not reported in original source; calculated by assuming that the standard error is equal to 10% of the mean.

Results of the Cost-Effectiveness Analysis

Base-Case Results

The model shows that imaging all patients with MRI results in the greatest number of correctly identified cases of SOLs and vascular dementia. The model also shows that treating individual patients with SOLs results in a greater gain in length and quality of life compared with treating those with AD and vascular dementia. However, people with SOLs make up only a small percentage of those with mild to moderate dementia. As a result, the greatest average QALY gain across the population is realized by correctly identifying people with AD, the most common type of dementia. Therefore, the strategy with the greatest combined specificity—CCC with CT followed by MRI to rule out SOLs—results in the greatest number of QALYs at the lowest cost. It is said to be the dominant strategy. Figure 10 presents model results on the incremental cost-effectiveness plane, and Table 21 reports total and incremental costs and QALYs.

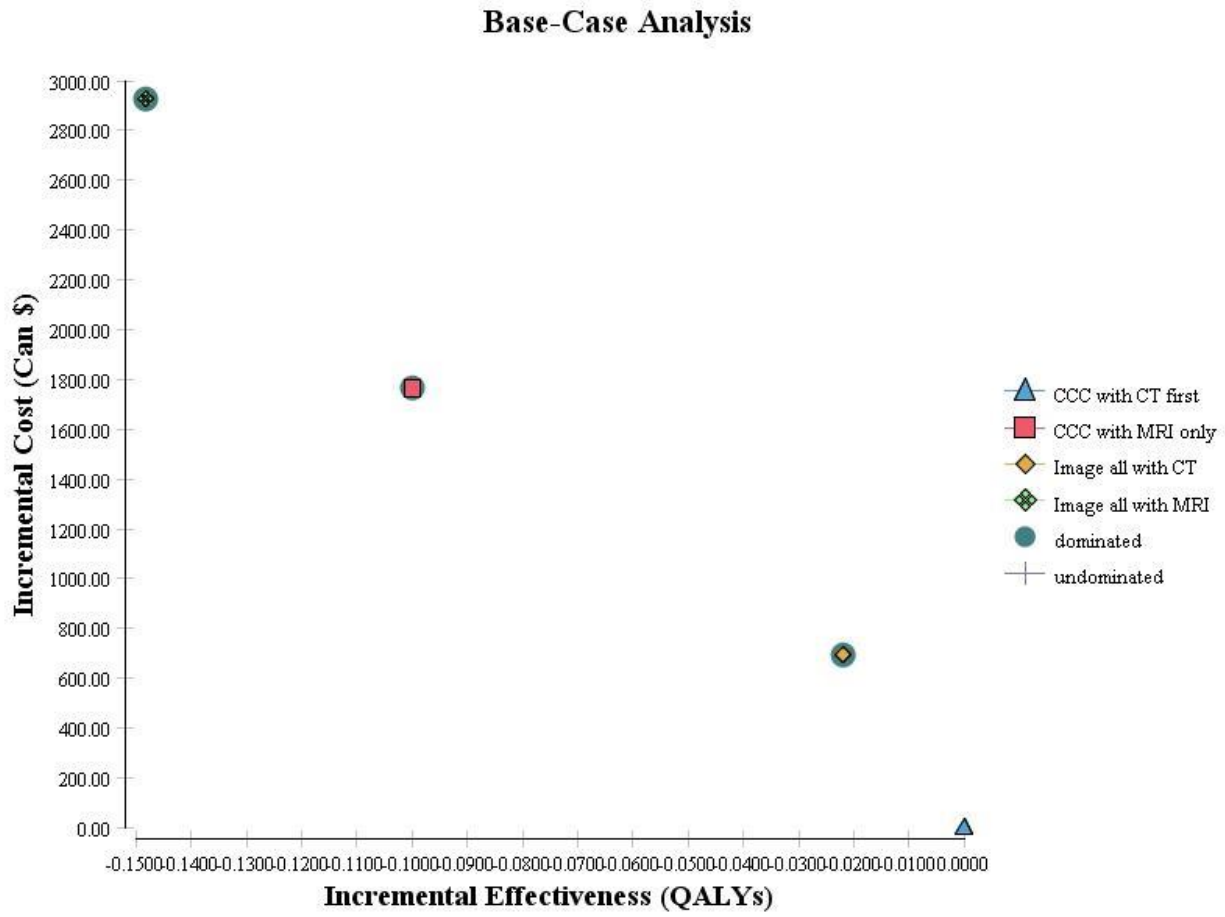

Figure 10: Incremental Costs and QALYs of Alternative Imaging Strategies

Abbreviations: CCC, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia; CT, computed tomography; MRI, magnetic resonance imaging; QALY, quality-adjusted life-year.

Table 21: Deterministic Results of Base-Case Analysis

Strategy	Total Costs, $	Total QALYs	Δ Costs, $	Δ QALY	Cost per QALY Gained
CCC with CT followed by MRI	250,303	2.738	Baseline	Baseline	Baseline
Image all with CT followed by MRI	250,996	2.716	693	- 0.022	Dominated
CCC with MRI	252,069	2.638	4,699	- 0.062	Dominated
Image all with MRI	253,229	2.590	5,859	- 0.110	Dominated

Abbreviations: CCC, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia; CT, computed tomography; MRI, magnetic resonance imaging; QALY, quality-adjusted life-year.

Discounted and undiscounted costs, QALYs, and life-years associated with each cause of dementia and diagnostic outcome are shown in Table 22. The median survival of AD patients has been estimated at 11 years from onset of symptoms, and 6 to 7 years from diagnosis, (69;70) roughly matching the outcome of our model. People with AD gain an average of 0.084 QALYs as a result of AChEI treatment. Cardiovascular risk management results in an increase of 0.013 QALYs for people with vascular dementia. People correctly assessed and treated for SOLs experience a gain of 1.515 QALYs compared with those not treated.

Table 22: Consequences of Each Diagnostic Outcome (Deterministic Values)

	Discounted at an Annual Rate of 5%			Not Discounted		
Outcome	Costs, $	QALYs	Life-Years	Costs, $	QALYs	Life-Years
NPH						
Correctly identified	159,410	3.238	6.469	243,527	4.531	9.330
Not identified	75,949	0.875	2.160	85,782	0.968	2.414
SDH						
Correctly identified	67,268	3.033	5.026	93,493	4.236	7.025
Not identified	114,701	1.228	3.143	137,555	1.428	3.711
BT						
Correctly identified	25,284	0.427	0.894	33,632	0.495	1.095
Not identified	4,722	0.155	0.259	4,775	0.157	0.263
AD						
All treated with AChEI	204,366	2.938	6.522	289,757	3.770	8.744
Some treated with AChEI*	202,584	2.911	6.488	287,327	3.734	8.694
Not treated	199,135	2.854	6.418	282,171	3.660	8.587
Mixed AD/VaD						
All treated with AChEI antiplatelets adjusted	339,214	2.736	7.160	513,286	3.669	10.099
All treated with AChEI; no antiplatelet adjustment	320,156	2.732	7.164	514,609	3.666	10.1065
VaD						
Antiplatelets adjusted	359,043	3.419	8.113	573,193	4.805	11.941
No antiplatelet adjustment	360,852	3.417	8.119	575,977	4.802	11.951

Abbreviations: AChEI, acetylcholinesterase inhibitors; AD, Alzheimer disease; BT, brain tumour; NPH, normal-pressure hydrocephalus; SDH, subdural hematoma; QALY, quality-adjusted life-year; VaD, vascular dementia.

The probability that each strategy will result in the correct identification of SOL (true positive) is shown in the first section of Table 23. Because each strategy was evaluated in terms of its ability to distinguish potentially treatable SOLs from VaD and AD, these outcomes were grouped together under "false positive" and "true negative." The second section of Table 23 presents the probability that each strategy will accurately distinguish VaD (true positive) from AD (true negative). The overall probability of correctly distinguishing SOLs and VaD from AD is presented in the last section of Table 23.

Table 23: Probability of Each Diagnostic Outcome (Deterministic)

Strategy	True Positive, %	False Positive, %	True Negative, %	False Negative, %	Check, %	
SOL versus VaD and AD					**TP + FN**	**FP + TN**
Image all with MRI	3.90	1.55	94.25	0.30	4.20	95.80
CCC with MRI	3.08	1.22	94.58	1.12	4.20	95.80
Image all with CT followed by MRI	3.04	0.24	95.56	1.16	4.20	95.80
CCC with CT followed by MRI	2.40	0.19	95.61	1.80	4.20	95.80
VaD versus AD					**TP + FN**	**FP + TN**
Image all with MRI	32.84	44.17	16.50	2.30	35.13	60.67
CCC with MRI	25.94	34.94	25.72	9.19	35.13	60.67
Image all with CT followed by MRI	26.42	23.26	37.41	8.71	35.13	60.67
CCC with CT followed by MRI	20.88	18.40	42.26	14.26	35.13	60.67
SOL and VaD versus AD					**TP + FP + TN + FN,**	
Image all with MRI	36.74	44.17	16.50	2.60	100.0	
CCC with MRI	29.02	34.94	25.72	10.31	100.0	
Image all with CT followed by MRI	29.46	23.26	37.41	9.87	100.0	
CCC with CT followed by MRI	23.28	18.40	42.26	16.06	100.0	

Abbreviations: AD, Alzheimer disease; CCC, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia; CT, computed tomography; FN, false negative; FP, false positive; MRI, magnetic resonance imaging; SOL, space-occupying lesion; TN, true negative; TP, true positive.

Table 24 shows the up-front, per-patient cost of imaging and AChEI treatment in each strategy. As expected, imaging all patients with MRI is associated with the greatest cost. Using the CCC guidelines to assess patient risk reduces this cost by 21%. However, if we assume that patients who do not receive neuroimaging are instead treated with AChEIs, the total cost savings associated with this strategy is reduced. A similar pattern is seen in the CT-first strategies, which must also account for the cost of MRI for those who test positive for SOLs according to CT.

Table 24: Initial Per-Patient Cost of Imaging and AChEI Treatment for Each Strategy (Deterministic)

Strategy	Initially Imaged, % of Cohort	Cost of Imaging Modality, $	First-Line AChEI, % of Cohort	6-Week Cost of AChEI Treatment, $	Secondary MRI, % of Cohort	Total Cost per Patient (Cycle 1), $
Image all with MRI	100.0	880	0.0	NA	0.0	880
CCC with MRI	79.0	880	21.0	209	0.0	761
Image all with CT followed by MRI	100.0	518	0.0	NA	18.0	669
CCC with CT followed by MRI	79.0	518	21.0	209	14.2	599

Abbreviations: AChEI, acetylcholinesterase inhibitors; CCC, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia; CT, computed tomography; MRI, magnetic resonance imaging.

Sensitivity Analyses

Sensitivity analyses are described below, and results are reported according to their corresponding number in Table 25. The impact of each sensitivity analysis on the results of the model can be seen by comparing the results of each analysis with the baseline model result (reported in the first row of Table 25).

Specificity of MRI

The base-case model uses an estimate of specificity that appears to be derived from the MR image independent of clinical contextualization. In practice, we would expect MRI plus clinical assessment to be the gold standard for the diagnosis of vascular dementia and space occupying lesions, resulting in a greater specificity than reported in the literature. A threshold analysis was run to determine the value at which a change in strategy was indicated.

1. The results showed that when MRI had a specificity of 64% for detecting vascular dementia, the most effective strategy was CCC with MRI.

2. At a specificity of 85%, imaging all patients with MRI became most effective, but that strategy then had an ICER of approximately $2 million compared to CCC with MRI.

Treatment of people not eligible for imaging according to CCC

3. In the base-case analysis, all those who are not eligible for imaging under CCC criteria are assumed to receive AChEI treatment. If we alter this assumption so that only half of these people receive AChEIs, the most effective and least costly strategy is to image all patients with CT.

Treatment of people with false positive diagnosis of SOL

4. The base-case model assumes that those with false positive diagnosis of SOL do not receive treatment for their underlying AD and vascular disease. If we remove this assumption and provide these patients with correct care (i.e., assume they are not erroneously treated for space-occupying lesions), the conclusions of the model are unchanged.

AChEI treatment effectiveness

5. The landscape of treatments for dementia is rapidly evolving. In the future, more efficacious treatments might become available. These treatments may or may not have greater costs than current treatments. If the effectiveness of the treatment is increased by half (i.e., those on treatment transition from mild and moderate to moderate and severe health states at 25% the rate of those not on treatment), the QALYs

associated with the CCC-with-CT strategy increase, as the QALYs gained among people who are treated without imaging also increase.

6. If we decrease the effectiveness of these drugs by half, the opposite effect is observed. However, CCC with CT remains the most effective strategy.

Prevalence of SOL

7. One-way sensitivity analyses were undertaken to explore the impact of varying the prevalence of each cause of dementia between the upper and lower reported values. When the prevalence of SOL was set equal to that observed in tertiary care settings (9%), CCC with CT first remains the dominant strategy.

Time horizon

8. Most previous models in this field have used time horizons of 18 months to 3 years. This is in part due to the short duration of the clinical effectiveness trials that these models have been designed to assess. If we limit the duration of the model to a 2-year time horizon, CCC with CT remains the dominant strategy.

Table 25: Sensitivity Analyses

	Optimal Strategy	Total Costs, $	Total QALYs	Δ Costs	Δ QALYs	Cost per QALY Gained
Base-case analysis						
Base case	CCC with CT	250,303	2.738	Baseline	Baseline	Dominant
Sensitivity analyses[a]						
1	CCC with MRI	250,277	2.760	Baseline	Baseline	Dominant
2	CCC with MRI	249,358	2.822	Baseline	Baseline	Baseline
3	Image all with CT	250,996	2.716	Baseline	Baseline	Dominant
4	CCC with CT	250,317	2.739	Baseline	Baseline	Dominant
5	CCC with CT	250,438	2.767	Baseline	Baseline	Dominant
6	CCC with CT	250,162	2.711	Baseline	Baseline	Dominant
7	CCC with CT	242,015	2.684	Baseline	Baseline	Dominant
8	CCC with CT	45,500	0.925	Baseline	Baseline	Dominant

Abbreviations: CCC, Canadian Consensus Conference on the Diagnosis and Treatment of Dementia; CT, computed tomography; MRI, magnetic resonance imaging; QALY, quality-adjusted life-year.

[a]Numbers correspond to descriptions of each analysis in text.

Budget Impact Analysis

The expert panel indicated that OHTAC recommendations on the appropriate use of neuroimaging in the diagnosis of dementia reflect current practice in Ontario. (18) Therefore, implementation of those recommendations is expected to be cost neutral.

Limitations

The lack of a "gold standard" modality for the diagnosis of dementia results in limitations intrinsic to the dementia literature. Estimates of diagnostic accuracy of the CCC guideline were assessed using CT, while studies assessing the diagnostic utility of neuroimaging evaluated these modalities against clinical assessments. As a result, there was a degree of uncertainty in the estimates used to inform our analysis that could not be accounted for with probabilistic analysis.

Currently, AChEIs are only licensed for use in people with mixed VaD and AD in Canada. In the French study used to inform progression of vascular dementia, approximately one-third of people with VaD were also receiving AChEI treatment. (40) The model conservatively assumes that only these patients experience benefit with treatment. If all patients with VaD in fact stand to benefit from AChEIs, the results of the model may change.

In accordance with the perspective of the Ministry of Health and Long-Term Care, indirect costs relating to patients' lost income and the impact of dementia on families and informal carers have not been included. However, we know that the social costs incurred by patients with dementia are large. (71) People with dementia may experience difficulties in the working environment, face challenges managing their finances, become less able to self-manage other health issues, and become dependent on family members for care. There is also a rise in traffic accidents in the elderly associated with dementia. None of these indirect outcomes were included in the current analysis.

The model was not designed to assess the impact of early diagnosis or treatment of patients with dementia, nor does it account for undiagnosed cases or cases of mild cognitive impairment. It is estimated that dementia is undiagnosed in up to two-thirds of people who suffer from it. (72) These conditions also carry high direct and indirect costs. The optimal diagnostic pathway for these patients would benefit from further analysis.

It should be noted that neuroimaging is not only undertaken to provide information to guide treatment; it can also provide valuable prognostic information for the patient and their family. The model does not account for patient preferences as to how desirable it is to know the result of such tests or the concomitant emotional, cognitive, and behavioural outcomes conferred by testing.

The model did not include adverse events associated with AChEIs. Although previous studies have found that models are somewhat sensitive to changes in adverse events, the expert panel indicated that this is not an issue with current drugs. This is confirmed by a Cochrane meta-analysis which found no difference in adverse events between donepezil and placebo. (73) Adverse events may become a consideration in future if new drugs with significant side-effect profiles become available.

It is possible that we have underestimated the benefit associated with cardiovascular risk factor modification in people with vascular disease diagnosed using MRI. For example, we have not accounted for modifications in blood pressure, blood sugar, or cholesterol that may arise from these diagnoses. These measures should be taken in every patient. However, clinicians often report that steps are not taken until a diagnosis of cerebrovascular disease is made. In addition, we did not account for the occurrence of Huntington disease, Creutzfeldt-Jakob disease, and frontotemporal dementia for the following reasons: Huntington usually affects younger patients than are included in this model; Creutzfeldt-Jakob disease is extremely rare and generally rapidly fatal; and frontotemporal dementia responds to the same treatments as AD. As a result, these omissions are unlikely to affect the outcomes of the model.

Conclusions

No recent published studies have evaluated the cost-effectiveness of different clinical prediction rules for assessing the appropriateness of neuroimaging for people with mild to moderate dementia or compared the cost-effectiveness of different structural imaging modalities in this population. Since 2000, 2 cost-utility studies and 1 clinical decision analysis have evaluated the benefit of adding functional neuroimaging to a baseline strategy of American Academy of Neurology (AAN) guidelines with CT as the imaging modality. (14-16) However, the evaluated imaging modalities are not licensed for the diagnosis of dementia in Canada, and a no-imaging/treat-all strategy was deemed an unsuitable comparator under current practice.

We developed a probabilistic Markov model to weigh the costs and consequences associated with prediction rules from the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCC), compared with imaging all patients. For patients eligible for structural imaging, we also compared the use of MRI as a first-line imaging modality with CT followed by MRI for those with suspected space-occupying lesions (SOL).

The results of the model show that imaging all patients with MRI results in the greatest number of correctly diagnosed cases of SOL and vascular dementia. Yet, because the prevalence of these conditions is relatively low, correctly identifying and treating those with AD results in the greatest QALY gain at the population level. Therefore, assessing patients for imaging according to the CCC guidelines and then using CT followed by MRI for those with suspected SOL is the most effective strategy because it is the most specific. It is also the least costly.

However, the results of the model are highly sensitive to the specificity of MRI. If we assume that MRI with clinical assessment represents the gold standard for diagnosis, the results of the model are very different. At a specificity of 64%, the most cost-effective strategy is CCC with MRI. At a specificity of 85%, imaging all patients with MRI is most effective, but with an incremental cost-effectiveness ratio of more than $2 million, this strategy would not be considered cost-effective.

The expert panel emphasized that practitioners, patients, and families place a high value on ruling out diagnoses of potentially treatable disease with a high degree of certainty. The results of MRI are thought to provide an important source of reassurance, allowing the patient to participate in actively planning for future care, including arranging legal and financial documents such as wills and advance directives. However, these factors are difficult to quantify and have not been incorporated into the model. Although methods of empirically incorporating "value" into "values" is an area of ongoing research, at the moment these factors must be considered as part of a broader ethical and societal decision making framework.

The low tolerance for risk regarding misdiagnoses of SOLs is reflected in the updated (2001) AAN guidelines. (5) In 1997, Chui and Zhang (19) studied the outcome of the 1994 AAN guidelines, which then recommended a selective approach to neuroimaging. They found a false negative rate of 5% and false positive rate of 36%. (19) According to Clarfield, (22) these data prompted the AAN to change its recommendation to a near-universal neuroimaging policy. Similarly, the authors of the study that informed the diagnostic accuracy of the CCC guidelines concluded that if the detection of strokes is also considered important, clinical prediction rules do not give satisfactory guidance for the management of patients with mild to moderate dementia and all should be considered for neuroimaging. (21)

Those in favour of an image-all strategy point out that limited resource use is the only obstacle to a near-universal strategy. (74) Despite limited surgical efficacy of treatment for SOLs, proponents cite studies

that show there is little risk involved in treating these patients and benefits are realized by reductions in mortality and cognitive decline. Critics argue that focusing on these rare conditions may do more harm than good in a population of elderly patients with dementia. Opponents to routine neuroimaging have cited the ability of clinical prediction rules to identify patients with SOLs, thereby reducing the error associated with imaging. (2;3;6) Our analysis supports both positions: at the individual level, patients with SOLs have the most to gain from a comprehensive MRI assessment; however, from a utilitarian perspective, assessing risk based on clinical prediction rules followed by CT offers a greater total gain at a lower cost.

The major strength of decision analysis is that it offers an explicit and systematic approach to decision making in the context of uncertainty. Even when the inputs and structure of the model may be incompletely supported by data, the decision analysis process itself can be valuable in identifying important areas of uncertainty and directing efforts toward acquiring information needed to address the key questions of interest. (66)

This analysis has revealed the difficulty of diagnosing dementia when there is no "gold standard" test against which to compare competing methods and modalities. It has also highlighted the lack of natural history and treatment efficacy data for vascular dementia and dementia caused by space-occupying lesions. As the results are sensitive to these data, the model should be considered a framework for assessing uncertainty in the evidence base rather than providing a definitive answer to the question posed.

Acknowledgements

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Expert Advisory Panel for Appropriate Utilization of Medical Imaging for the Diagnostic Work-Up in Patients with Dementia

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Dr James Sahlas	McMaster University, Division of Neurology, Department of Medicine	Associate Professor
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Ministry of Health Representative		
Dr Garry Salisbury	Ministry of Health and Long-Term Care, Division of Negotiation and Accountability Management	Senior Medical Consultant

Appendices

Appendix 1: Literature Search Strategies

Search date: February 22, 2013
Databases searched: Ovid MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, Embase; Cochrane; Centre for Reviews and Dissemination (CRD) database
Limits: 2000-present; English; NOT case reports, comments, editorials, letters
Filters: economic
Question:
Appropriate use of imaging in the diagnostic workup for dementia

Database: Ovid MEDLINE(R) <1946 to February Week 2 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 21, 2013>, Embase <1980 to 2013 Week 07>
Search Strategy:

#	Searches	Results
1	exp Dementia/	312830
2	exp Cognition Disorders/ use mesz	54697
3	exp cognitive defect/ use emez	84437
4	(dementi* or alzheimer* or predementia* or pre-dementia* or ((dementi* or alzheimer*) adj2 (revers* or early))).ti,ab.	273690
5	or/1-4	469205
6	exp Tomography, X-Ray Computed/ use mesz or exp computer assisted tomography/ use emez	817744
7	exp Magnetic Resonance Imaging/ use mesz or exp nuclear magnetic resonance imaging/ use emez	747433
8	exp Positron-Emission Tomography/	99584
9	exp Neuroimaging/	160139
10	(computed tomograph* or fluorodeoxyglucose* or fludeoxyglucose* or neuroimag* or 18F-FDG or FDG-PET or ct scan* or EBCT or MDCT).ti,ab.	497731
11	or/6-10	1648527
12	5 and 11	52004
13	exp "Predictive Value of Tests"/ use mesz or exp predictive value/ use emez	155203
14	exp decision support techniques/ use mesz or exp medical decision making/ use emez	116786
15	exp disease progression/ use mesz	104142
16	exp early diagnosis/	75392
17	exp likelihood functions/ use mesz or exp maximum likelihood method/ use emez	19708
18	exp odds ratio/ use mesz	51173
19	exp Diagnosis, Differential/ use mesz or exp differential diagnosis/ use emez	663742
20	*"Sensitivity and Specificity"/	848
21	exp Decision Trees/	13370
22	(predict* or decision making or decision support* or likelihood ratio* or clinical utilit* or differential diagnos* or early diagnos*).ti,ab.	2280095
23	or/13-22	3141781
24	12 and 23	12283
25	exp Economics/ use mesz or exp Models, Economic/ use mesz or exp Resource Allocation/ use mesz or exp "Value of Life"/ use mesz or exp "Quality of Life"/ use mesz	565122
26	exp "Health Care Cost"/ use emez or exp Health Economics/ use emez or exp Resource Management/ use emez or exp Economic Aspect/ use emez or exp Economics/ use emez or exp Quality Adjusted Life	1295876

	Year/ use emez or exp Socioeconomics/ use emez or exp Statistical Model/ use emez or exp "Quality of Life"/ use emez	
27	(econom* or cost* or budget* or pharmacoeconomic* or pharmaco-economic* or valu*).ti.	492706
28	((cost$ adj benefit$) or costbenefit$ or (cost adj effective$) or costeffective$ or econometric$ or life value or quality-adjusted life year$ or quality adjusted life year$ or quality-adjusted life expectanc$ or quality adjusted life expectanc$ or sensitivity analys$ or "value of life" or "willingness to pay").ti,ab.	198190
29	ec.fs.	3480133
30	or/25-29	5406927
31	24 and 30	2106
32	limit 31 to english language	1943
33	limit 32 to yr="2000 -Current"	1822
34	limit 33 to (case reports or comment or congresses or editorial or letter or conference abstract or conference paper or conference proceeding) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,Embase; records were retained]	230
35	33 not 34	1592
36	remove duplicates from 35	1541

Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Dementia] explode all trees	3282
#2	MeSH descriptor: [Cognition Disorders] explode all trees	2279
#3	(dementi* or alzheimer* or predementia* or pre-dementia* or ((dementia* or alzheimer*) near/2 (revers* or early))):ti (Word variations have been searched)	5324
#4	#1 or #2 or #3	7838
#5	MeSH descriptor: [Tomography, X-Ray Computed] explode all trees	3221
#6	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees	4548
#7	MeSH descriptor: [Positron-Emission Tomography] explode all trees	755
#8	MeSH descriptor: [Neuroimaging] explode all trees	1745
#9	(computed tomograph* or fluorodeoxyglucose* or fludeoxyglucose* or neuroimag* or 18F-FDG or FDG-PET or ct scan* or EBCT or MDCT):ti	1496
#10	#5 or #6 or #7 or #8 or #9	9428
#11	MeSH descriptor: [Predictive Value of Tests] explode all trees	5118
#12	MeSH descriptor: [Decision Support Techniques] explode all trees	2714
#13	MeSH descriptor: [Disease Progression] explode all trees	4529
#14	MeSH descriptor: [Early Diagnosis] explode all trees	556
#15	MeSH descriptor: [Likelihood Functions] explode all trees	314
#16	MeSH descriptor: [Odds Ratio] explode all trees	2622
#17	MeSH descriptor: [Diagnosis, Differential] explode all trees	1345
#18	MeSH descriptor: [Sensitivity and Specificity] explode all trees	13747
#19	MeSH descriptor: [Decision Trees] explode all trees	766
#20	(predict* or decision making or decision support* or likelihood ratio* or clinical utilit* or differential diagnos* or early diagno*):ti (Word variations have been searched)	8446
#21	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20	30739
#22	#4 and #10 and #21	118
#23	MeSH descriptor: [Economics] explode all trees	20383
#24	MeSH descriptor: [Models, Economic] explode all trees	1505
#25	MeSH descriptor: [Resource Allocation] explode all trees	124
#26	MeSH descriptor: [Value of Life] explode all trees	142
#27	MeSH descriptor: [Quality of Life] explode all trees	12209
#28	(econom* or cost* or budget* or pharmacoeconomic* or pharmaco-economic* or valu*):ti (Word variations have been searched)	21015
#29	((cost* near benefit*) or costbenefit* or (cost near effective*) or costeffective* or econometric* or life value or quality-adjusted life year* or quality adjusted life year* or quality-adjusted life expectanc* or quality adjusted life expectanc* or sensitivity analys* or "value of life" or "willingness to pay"):ti,ab,kw (Word variations have been searched)	32095
#30	#23 or #24 or #25 or #26 or #27 or #28 or #29	52438
#31	#22 and #30 from 2000 to 2013	31

CRD

Line	Search	Hits
1	MeSH DESCRIPTOR dementia EXPLODE ALL TREES	394
2	MeSH DESCRIPTOR cognition disorders EXPLODE ALL TREES	157
3	(dementi* or alzheimer* or predementia* or pre-dementia* or ((dementia* or alzheimer*) adj2 (revers* or early))):TI	492
4	#1 OR #2 OR #3	659
5	MeSH DESCRIPTOR tomography, x-ray computed EXPLODE ALL TREES	667
6	MeSH DESCRIPTOR magnetic resonance imaging EXPLODE ALL TREES	531
7	MeSH DESCRIPTOR positron-emission tomography EXPLODE ALL TREES	237
8	MeSH DESCRIPTOR neuroimaging EXPLODE ALL TREES	50
9	(computed tomograph* or fluorodeoxyglucose* or fludeoxyglucose* or neuroimag* or 18F-FDG or FDG-PET or ct scan* or EBCT or MDCT):TI	442
10	#5 OR #6 OR #7 OR #8 OR #9	1339
11	MeSH DESCRIPTOR predictive value of tests EXPLODE ALL TREES	723
12	MeSH DESCRIPTOR decision support techniques EXPLODE ALL TREES	1231
13	MeSH DESCRIPTOR disease progression EXPLODE ALL TREES	439
14	MeSH DESCRIPTOR early diagnosis EXPLODE ALL TREES	176
15	MeSH DESCRIPTOR likelihood functions EXPLODE ALL TREES	65
16	MeSH DESCRIPTOR odds ratio EXPLODE ALL TREES	841
17	MeSH DESCRIPTOR diagnosis, differential EXPLODE ALL TREES	171
18	MeSH DESCRIPTOR sensitivity and specificity EXPLODE ALL TREES	2947
19	MeSH DESCRIPTOR decision trees EXPLODE ALL TREES	668
20	(predict* or decision making or decision support* or likelihood ratio* or clinical utilit* or differential diagnos* or early diagno*):TI	657
21	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	5943
22	#4 AND #10 AND #21	8
23	MeSH DESCRIPTOR Economics EXPLODE ALL TREES	13237
24	MeSH DESCRIPTOR Models, Economic EXPLODE ALL TREES	1417
25	MeSH DESCRIPTOR Resource Allocation EXPLODE ALL TREES	75
26	MeSH DESCRIPTOR Value of Life EXPLODE ALL TREES	116
27	MeSH DESCRIPTOR Quality of Life EXPLODE ALL TREES	1744
28	(econom* or cost* or budget* or pharmacoeconomic* or pharmaco-economic* or valu*):TI	12194
29	((cost* adj benefit*) or costbenefit* or (cost adj effective*) or costeffective* or econometric* or life value or quality-adjusted life year* or quality adjusted life year* or quality-adjusted life expectanc* or quality adjusted life expectanc* or sensitivity analys* or "value of life" or "willingness to pay")	19111
30	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	21329
31	#22 AND #30	2
32	(#31) FROM 2000 TO 2013	2

Appendix 2: Characteristics and Results of Studies Included in Economic Literature Review

Table A1: McMahon et al, 2000

<table>
<tr><th colspan="4">McMahon PM, Araki SS, Neumann PJ, Harris GJ, Gazelle GS. Cost-effectiveness of functional imaging tests in the diagnosis of Alzheimer disease. Radiology. 2000;217:58-68.</th></tr>
<tr><td colspan="4">Methods</td></tr>
<tr><td>Study details</td><td>Population</td><td colspan="2">Interventions</td></tr>
<tr><td>Type of economic analysis:
Cost-utility analysis
Study design: Markov decision model
Perspective:
United States, Societal
Time horizon:
18 months</td><td>People with mild to moderate dementia (with a 56% prevalence of Alzheimer disease [AD] and a ratio of mild to moderate AD of 1.5:1.0)
Mean age: 76 years
Male: NR</td><td colspan="2">Intvn 1: Standard examination (with CT)
Intvn 2: MRI plus concurrent DSC MRI for all patients
Intvn 3: Standard examination with CT plus visual SPECT only for patients with diagnosis of possible Alzheimer disease at standard examination.
Intvn 4: Standard examination with CT plus computed SPECT only for patients with diagnosis of possible Alzheimer disease at standard examination.</td></tr>
<tr><td colspan="4">Approach to analysis</td></tr>
<tr><td colspan="4">In specialized AD clinics, the standard diagnostic work-up was assumed to consist of a detailed history, assessment of cognition and functional status, laboratory testing and structural brain imaging with non-enhanced CT. The aim of the model was to compare the cost-effectiveness of strategies that add a functional neuroimaging test (such as PET or SPECT) to the conventional diagnostic work up for patients with dementia and suspected AD.
Patients began the model in the community setting and could transition to nursing home care depending on the disease state at each 6-week cycle. In the base case, all patients who received a diagnosis of AD received treatment with donepezil. Once a patient progresses to severe AD, no further treatment is given since there is no evidence of effectiveness in this group. (Patients with severe dementia were excluded from the initial population on the basis that donepezil hydrochloride is not indicated for the treatment of severe AD and because imaging was assumed to be unnecessary to confirm the diagnosis.)</td></tr>
<tr><td colspan="4">Results</td></tr>
<tr><td>Costs</td><td>Health outcomes</td><td colspan="2">Cost effectiveness</td></tr>
<tr><td>Currency and cost year:
1998 US dollars
Total costs (mean per person):
Intvn 1: $54,762
Intvn 2: $55,769
Intvn 3: $55,362
Intvn 4: $55,549
Incremental (2 – 1): $1, 007
Discount rate: 3%</td><td>Primary outcome:
QALYs
Total QALYs (mean per person):
Intvn 1: 0.9889
Intvn 2: 0.9910
Intvn 3: 0.9851
Intvn 4: 0.9888
Incremental (2 – 1): 0.0021
Discount rate: 3%</td><td colspan="2">Primary ICER:
Interventions 3 and 4 are dominated by intervention 2, which has a cost of $479,500 per QALY
Other:
Eliminating patient costs (e.g., travel and wages lost) resulted in a cost per QALY of $323,830.</td></tr>
<tr><td colspan="4">Interpretation</td></tr>
<tr><td colspan="2">Sensitivity analyses</td><td colspan="2">Limitations and Applicability</td></tr>
<tr><td colspan="2">Interventions:
The following additional strategies were included in the model in sensitivity analysis:
Intvn 5: CT + visual SPECT for all patients was dominated by standard examination.
Intvn 6: CT + computed SPECT for all patients had an ICER of $430,900.
Intvn 7: Hypothetical perfect test (with same cost as MRI plus DSC MRI; no second visit for functional imaging).</td><td colspan="2">In the base-case analysis, this study took a societal perspective. Given that our frame of reference is the Ontario health care system, the results of the sensitivity analysis (in which patient costs are eliminated) should be considered the more applicable of the 2 results.
The short time horizon of the analysis was a major limitation of this study.
The ratio of mild to moderate AD was explored in sensitivity analysis, but not the prevalence of AD within the mild to moderate dementia population. Because the</td></tr>
</table>

Intvn 8: Treat all patients (no imaging or lab tests). **Treatment effectiveness:** A hypothetical drug with a relative risk of progression from mild to moderate AD of 0.1 (compared to 0.5 in the base case) and risk ratio of transition from moderate to mild of 10.0 (compared to a baseline value 2.3) was evaluated. Strategy 2 was most effective with an ICER of $174,470. A second hypothetical drug with a relative risk of progression from mild to moderate AD of 0.25 (compared to 0.5 in the base case) and risk ratio of transition from moderate to mild of 5.0 (compared to a baseline value 2.3) was also evaluated. Strategy 2 was most effective with an ICER of $22,470. **Treatment duration:** If the treatment durations (and therefore time horizon) of treatment with donepezil was 6 or 12 months, strategy 2 was either dominated or had an ICER of over $3 million. As duration increased to 48 months, the ICER decreased to $58,930. **Disease progression:** Natural history transition probabilities were increased and decreased by 10% respective to base-case values. The probability of death from other causes was set to 0.018, slightly lower than base case.	base case assumes that patients are presenting to a specialized AD centre, with a prevalence of 56%, the results may not be applicable across all health care settings.
Data sources	
Clinical effectiveness: The prevalence of AD in people who present to the disease centre was 56% (derived from data in which 64% of people with dementia had a diagnosis of AD and 90% of these diagnoses were confirmed at autopsy). The probability of death for patients without AD was obtained from the National Centre for Health Statistics; the annual probability of death at age 76 years was used as this is the mean age of patients at presentation to the institution at which the study is based. Donepezil treatment was modelled as a 50% reduction in the probability of transition from mild to moderate, based on a study by Rogers et al, 1998 (75). **Costs:** Resource use for the initial diagnostic workup was estimated to include 2 physician consultations (internal medicine and neurology), a series of lab tests, and structural imaging (CT or MR), and was based on the literature and an assessment at Massachusetts General Hospital. Costs were based on hospital and Medicare data. The initial work-up was estimated to take 1 day; travel, lunch, and wages were calculated per 8-hour day. The model uses 6-week cycles. **Quality of life:** For people without AD, utility (0.826) was based on a community survey by Fryback et al 1993. (76) Weights for people at each disease stage and care setting were based on HUI2 scores published by Neumann et al, 1999; (17) Neumann et al, 1998; (77) and Neumann et al, 1999. (78)	
Funding	
Study funding NR; lead author receives unrestricted funding from Pfizer, manufacturer of donepezil.	

Abbreviations: AD, Alzheimer disease; CT, computed tomography; DSC, dynamic susceptibility contrast magnetic resonance imaging; HUI, Health Utilities Index; ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; NR, not reported; PET, positron emission tomography; QALY, quality-adjusted life-year; SPECT, single-photon emission computed tomography.

Table A2: McMahon et al, 2003

McMahon PM, Araki SS, Sandberg EA, Neumann PJ, Gazelle GS. Cost-effectiveness of PET in the diagnosis of Alzheimer disease. Radiology. 2003;228(2):515-22.		
Methods		
Study details	**Population**	**Interventions**
Type of economic analysis: Cost-utility analysis **Study design:** Markov decision model **Perspective:** United States, Societal **Time horizon:** 18 months	Community dwelling adults with mild to moderate dementia. **Mean age:** NR **Male:** NR	**Intvn 1:** Standard examination (with CT) **Intvn 2:** DSC MRI **Intvn 3:** Standard examination with CT plus PET only for patients with diagnosis of possible Alzheimer disease (AD) at standard examination **Intvn 4:** Standard examination with CT plus compound SPECT only for patients with diagnosis of possible Alzheimer disease at standard examination **Intvn 5:** Hypothetical perfect examination strategy **Intvn 6:** Treat all patients
Approach to analysis		
The standard diagnostic work-up common to specialized AD clinics was assumed to consist of a detailed history, assessment of cognition and functional status, laboratory testing, and structural brain imaging with non-enhanced CT. The analysis was designed to compare strategies involving the use of either computed SPECT, dynamic susceptibility-weighted contrast MRI, or FDG PET as functional imaging additions to the standard clinical examination. Visual SPECT was not included in this analysis because it was dominated in all scenarios in the author's previous study. In the base case, PET or compound SPECT was performed on a second visit only on patients who received a diagnosis of possible or probable AD on the basis of the standard examination results. This model was similar in methods, structure, and inputs to that described by the authors in their 2000 paper, with the exception of the inclusion of PET as an intervention. The authors note that although new drugs (rivastigmine tartrate and galantamine hydrobromide) have been introduced for the treatment of AD since the publication of their last paper, they retained the use of donepezil for the base-case analysis due to the availability of robust evidence for the probability of transition between different disease states.		
Results		
Costs	**Health outcomes**	**Cost effectiveness**
Currency and cost year: 1999 US dollars **Total costs (mean per person):** **Intvn 1:** $56,859 **Intvn 2:** $57,877 **Intvn 3:** $58,590 **Intvn 4:** $58,872 **Intvn 5:** $57,876 **Intvn 6:** $57,339 **Incremental (6 – 1):** $480 **Discount rate:** 3%	**Primary outcome:** QALYs **Total QALYs (mean per person):** **Intvn 1:** 0.7092 **Intvn 2:** 0.7109 **Intvn 3:** 0.7063 **Intvn 4:** 0.7093 **Intvn 5:** 0.7138 **Intvn 6:** 0.7126 **Incremental (2 – 1):** 0.0034 **Discount rate:** 3%	**Primary ICER:** Interventions 3 and 4 are dominated by interventions 2, 5 and 6. Intervention 5 is the most effective of the 3 non-dominated strategies, with a cost of $221,100 per QALY gained. Intervention 6 is the next most effective, at a cost of $141,200 per QALY gained. Intervention 2 is the least effective of the 3, with a cost of $598,800 per QALY gained.
Interpretation		
Sensitivity analyses		**Limitations and Applicability**
A hypothetical perfect examination with a cost equal to MRI dominated all functional strategies but resulted in a QALY gain only 0.0046 greater than standard examination, resulting in an ICER of $221,100. To be cost saving relative to standard examination, the perfect		In the base-case analysis, this study took a societal perspective. The ratio of mild to moderate AD was explored in sensitivity analysis, but not the prevalence of AD within the mild to moderate dementia population. Because the

examination must cost $427 or less. The cost-effectiveness of MRI was improved with increasing hypothetical drug effectiveness. If it is assumed that inappropriate treatment with donepezil leads to decreased quality of life from side effects, MRI ICER is $74,400. In scenarios involving the use of PET only in patients with positive standard examination results, the addition of PET was dominated by either standard examination or MRI. In contrast, when PET was performed in patients with negative standard examination results, the incidence of false negatives was reduced and the overall effectiveness of this strategy increased. If the HUI2 (rather than 3) was used to inform utilities, the ICER for MRI increased to $518,200. Varying the cost of imaging by +/- 50% or excluding patient costs and the cost of caregivers' time changed the results of the analysis.	base case assumes that patients are presenting to a specialized AD centre, with a prevalence of 56%, the results may not be applicable across all health care settings.
Data sources	
Clinical effectiveness: The natural history of AD was based on a model by Neumann et al, 1999. (17) The effectiveness of each intervention was based on estimates of sensitivity and specificity from the literature; it is not clear whether these were identified systematically. **Costs:** The total cost of a standard examination was estimated to be $533. The cost of PET ($1,671) was obtained from administrative data at the Massachusetts General Hospital. The cost of computer-aided data manipulation ($92) was added to the cost of computed SPECT ($2,083) for a total cost of $2,175. The cost of MRI plus dynamic susceptibility weighted contrast enhanced MRI ($1,444) was estimated to be equal to the Medicare reimbursements for MRI with and without contrast material plus the costs for a computerized 3-dimensional reconstruction. **Quality of life:** HRQOL weights for people with and without AD were based on the HUI3. (79;80) Utilities for age-matched community-dwelling Canadians were derived from literature by Neumann et al, 1999. (78)	
Funding	
Study funding NR; authors report receiving funding from the National Cancer Institute, National Library of Medicine, and United States Army.	

Abbreviations: AD, Alzheimer disease; CT, computed tomography; DSC, dynamic susceptibility contrast magnetic resonance imaging; FDG PET, fluorodeoxyglucose 18F positron emission tomography; HRQOL, health-related quality of life; HUI, Health Utilities Index; ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; NR, not reported; PET, positron emission tomography; QALY, quality-adjusted life-year; SPECT, single-photon emission computed tomography.

Table A3: Kulasingam et al, 2003

Kulasingam SL, Samsa GP, Zarin DA, Rutschmann OT, Patwardhan MB, McCory DC, Schmechel DE, Matchar DB. When should functional neuroimaging techniques be used in the diagnosis and management of Alzheimer's dementia? A decision analysis. Value in Health. 2003;6(5):542-50.		
Methods		
Study details	**Population**	**Interventions**
Type of economic analysis: Clinical utility decision analysis **Study design:** Decision analytic model **Perspective:** Health care payer **Time horizon:** Lifetime	Strategies were evaluated within 3 patient populations: mild dementia, mild cognitive impairment, and asymptomatic with an increased risk of Alzheimer disease (AD) **Mean age:** ≥ 65 years **Male:** NR	**Intvn 1:** Standard diagnosis as recommended by the American Academy of Neurology (AAN), consisting of a complete history, physical and neuropsychiatric evaluation, and structural imaging (specifically CT) tests to rule out non-AD causes of dementia. **Intvn 2:** PET scanning was added to the standard treatment strategy. **Intvn 3:** Empiric treatment, whereby all asymptomatic patients were treated
Approach to analysis		
The aim of this paper was to compare standard clinical evaluation (defined as complete history, physical and neuropsychiatric evaluation, and CT) vs. functional neuroimaging (PET scanning) vs. clinical evaluation alone, to determine which strategy maximizes health outcomes. The prevalence of AD in people with mild dementia was assumed to be 56%. For the asymptomatic population, the cumulative lifetime risk for people with a family history of AD was assumed to be 50%. Natural history transition probabilities were based on data from the Consortium to Establish a Registry for Alzheimer's disease (CERAD) and expert opinion. The effect of treatment for AD was estimated as a risk ratio of 0.72 for the development of more severe AD. Treatment began at age 65 for all patients, continued for 18 months, and was discontinued on development of severe dementia.		
Results		
Costs	**Health outcomes**	**Cost effectiveness**
Currency and cost year: NA **Total costs (mean per person):** **Intvn 1:** NA **Intvn 2:** NA **Incremental (2 – 1):** NA **Discount rate:** NA	**Primary outcome:** QALYs **Total QALYs (mean per person):** **Mild dementia:** **Intvn 1:** 4.10 **Intvn 2:** 4.09 **Intvn 3:** 4.02 **Incremental (2 – 1):** -0.01 **Asymptomatic with elevated risk:** **Intvn 1:** 12.25 **Intvn 2:** 12.23 **Intvn 3:** 12.11 **Incremental (2-1):** -0.02 **Discount rate:** 3%	**Primary ICER:** NA **Other:** The standard (AAN) diagnostic strategy resulted in the greatest QALY gain for both populations and was the preferred strategy across all outcomes (severe-dementia-free life-years and dementia-free life-years not reported in this table).
Interpretation		
Sensitivity analyses		**Limitations and Applicability**
The AAN diagnostic strategy remained the preferred strategy despite changes in the sensitivity and specificity of PET, prevalence of underlying AD, relative risk of progression as a result of treatment, length of efficacy of treatment, percentage of patients experiencing complications, and discount rates. However, when complications were fatal, the natural history (empiric treatment) option was preferred. To investigate the effect of treatment compliance, a series of hypothetical treatments with the potential for		The model assessed functional rather than structural imaging modalities and is therefore not directly relevant to our analysis; PET and SPECT are not approved for use for the diagnosis of dementia in Canada. Costs were not included in this study, only quality of life.

moderate to severe complications were modelled. If treatment complications resulted in greater disutility, the AAN + PET-based diagnosis was preferred. Treatment efficacy was explored by varying the relative risk of progression to severe dementia between 0 and 1 and utility of complications between 0 and 1. If treatment was very effective, the AAN strategy was preferred. If complications were severe, AAN-PET strategy was preferred.	
Data sources	
Clinical effectiveness: Estimates of PET sensitivity [86% (range 74%–92%)] and specificity [87% (range 78%–93%)] for people with mild dementia were based on a review and meta-analysis by Patwardham et al, 2003. (81) The same estimates were applied to the asymptomatic population for lack of other data. Treatment efficacy was modelled as a risk ratio of 0.72 for progression to more severe AD based on a trial by Mohs et al, 2001 (82) and Matchar et al, 2001. (83) It was assumed that 15% of patients experienced treatment complications with no long-term side effects, based on a study by Mohs et al, 2001. (82) **Costs:** Costs were not included in this study; clinical utility only. **Quality of life:** Health state utility values were obtained from a study by Neumann et al, 1999 (78); complications associated with treatment were assigned a disutility lasting a few days (source not reported).	
Funding	
Sponsored by the Agency for Healthcare Research and Quality.	

Abbreviations: AAN, American Academy of Neurology; AD, Alzheimer disease; CT, computed tomography; ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; NA, not available; NR, not reported; PET, positron emission tomography; QALY, quality-adjusted life-year.

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